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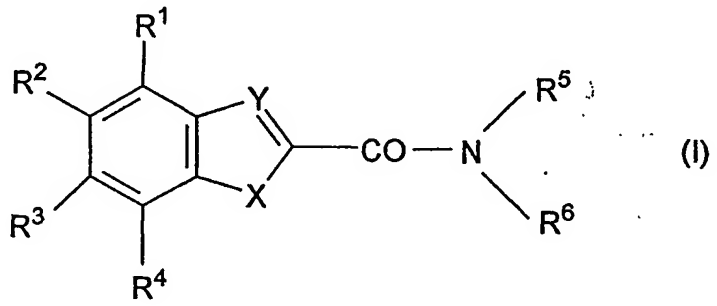
(54) Title: AMIDE DERIVATIVES AS NMDA RECEPTOR ANTAGONISTS

(57) Abstract: The invention relates to new NR2B selective NMDA receptor antagonist carboxylic acid amide derivatives of formula (I) as well as the recemates, optical antipodes and the salts thereof formed with acids and bases. Fruthermore objets of the present invention are the pharmaceutical compositions containing compounds of formula (I) or the salts thereof as active ingredients, as well as the synthesis of compounds of formula (I), and the chemical and pharmaceutical manufacture of medicaments containing these compounds, as well as the method of treatments with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament. The new carboxylic acid amide derivatives of formula (I) of the present invention are highly effective and selective antagonists of NMDA receptor, and moreover most of the compounds are selective antagonist of NR2B subtype of NMDA receptor.

AMIDE DERIVATIVES AS NMDA RECEPTOR ANTAGONISTS

The invention relates to new NMDA receptor antagonist carboxylic acid amide derivatives of formula (I)



(I)

- wherein

R^1, R^2, R^3 and R^4 independently are hydrogen or halogen atom, hydroxyl, nitro, amino, carboxyl, sulfamoyl [NH_2-SO_2-], cyano, carbamoyl [-CO-NH_2], hydroxycarbamoyl [-CO-NHOH], thiocarbamoyl [-CS-NH_2], amidino [-C=(NH)-NH_2], hydroxyamidino [-C=(NOH)-NH_2], formyl [-CHO], hydroxyimino-methyl [-CH=NOH], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkoxymethyl, halogenmethyl, tetrazolyl or imidazoline-2-yl group, or

C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_1-C_4 alkylsulfonamido – in given case substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido – in given case substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonyloxy, piperidyl-C_1-C_4 alkyl, phenyl or C_1-C_4 alkoxy groups, substituted by amino group, or

in given case benzoyloxy group substituted by halogen atom, C_1-C_4 alkyl, C_1-C_4 alkoxy or aliphatic or cyclic amino group, or

alkanoyloxy, alkanoyl-amido, benzamido, or benzenesulfonyl-amido group, substituted by aliphatic or cyclic amino group or

ureido [-NH-CO-NH_2] or thioureido group [-NH-CS-NH_2], substituted by C_1-C_4 alkyl or phenyl group or

in given case amidino group [-C(=NH)-NH_2], substituted on the primer amino by one or two C_1-C_4 alkyl group, wherein in given case the two C_1-C_4 alkyl groups together with the nitrogen atom between them can form a 5-7 membered heterocyclic ring, or

in given case ureidoimino-methyl [-CH=N-NH-CO-NH_2] or thio-ureidoimino-methyl group [-CH=N-NH-CS-NH_2], substituted by C_1-C_4 alkyl or phenyl group or

in given case aminoimino-methyl [-CH=N-NH_2] group substituted by a C_1-C_4 alkyl or phenyl group

with the restriction, that the meaning of at least one of R^1, R^2, R^3 and R^4 is different from hydrogen atom, and if the meaning of R^2 is amidino group, as well as the meaning of X is -NH- group, then the meaning of -$CONR^5R^6$ group is different from 4-benzyl-piperidino group, or

two of the neighboring R^1, R^2, R^3 and R^4 groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form a 4-7 membered homo- or heterocyclic ring, preferably pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

from among R^5 and R^6 one of them is hydrogen atom and then the other is phenyl-cyclohexyl group or C_1-C_4 alkyl group, substituted by one or two hydroxy, phenyl, hydroxyphenyl or halogenphenyl groups, or

R^5 and R^6 together with the nitrogen between them form a saturated or unsaturated, 4-6 membered heterocyclic ring, which is substituted by hydroxy group, and/or in given case phenyl or phenoxy, phenyl-(C_1-C_4 alkyl), phenyl-(C_1-C_4 alkoxy), phenoxy-(C_1-C_4 alkyl), anilino, phenyl-(C_1-C_4 alkylamino), [phenyl-(C_1-C_4 alkyl)]-amino, benzoyl, hydroxy-diphenylmethyl, C_1-C_4 alkoxycarbonyl-phenoxymethyl or

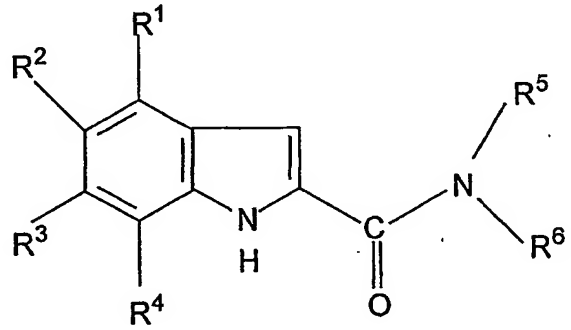
benzhydrylidene group, substituted on the aromatic ring by one or more halogen atom, cyano or hydroxy group, C_1-C_4 alkyl or C_1-C_4 alkoxy group,

the meaning of X and Y is independently oxygen, nitrogen or sulfur atom, as well as -CH=, -CH=CH-, -CH_2-, -SO-, -SO_2-, -NH- or -NR-group, wherein the meaning of R is hydrogen atom or C_1-C_4 alkyl group,

racemates, optical antipodes and the salts thereof formed with acids and bases.

As the invention relates also to the salts of compounds of formula (I) formed with acids or bases, especially the salts formed with pharmaceutically acceptable acids or bases, the meaning of compound of formula (I) is either the free compound or the salt even if it is not referred separately.

An especially significant group of the compounds of the invention are the compounds of the formula (Ia),



(Ia)

- wherein the meaning of R^1, R^2, R^3, R^4, R^5 and R^6 is as described for the formula (I).

Especially important carboxylic acid amide derivatives of formula (I) are the following:

1-(4-benzyloxypiperidine-1-yl)-1-(4,6-dihydroxy-1H-indole-2-yl)methanone,

1-(4-benzylpiperidine-1-yl)-1-(4,6-dihydroxy-1H-indole-2-yl)methanone,

1-(4-benzyloxypiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone,

1-(4-benzylpiperidine-1-yl)-1-(4-hydroxy-1H-indole-2-yl)methanone,

1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone,

1-(4-benzylpiperidine-1-yl)-1-(5-hydroxy-1H-indole-2-yl)methanone,

1-(6-hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyloxy)piperidine-1-yl)]methanone,

1-(4-benzylpiperidine-1-yl)-1-(5,7-dihydroxy-1H-indole-2-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-(4-phenoxymethylpiperidine-1-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyl)-4-hydroxypiperidine-1-yl)]methanone,
1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-7-methoxy-1H-indole-2-yl)methanone,
1-(6-acetoxy-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone,
1-[4-(4-fluorobenzylpiperidine-1-yl)]-1-(6-hydroxy-1H-indole-2-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-(4-phenoxypiperidine-1-yl)methanone,
1-[4-(4-fluorobenzylpiperidine-1-yl)]-1-(5-hydroxy-1H-indole-2-yl)methanone,
1-(4-hydroxy-1H-indole-2-yl)-1-(4-phenoxymethylpiperidine-1-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-(4-phenoxy-3,6-dihydro-2H-piridine-1-yl)methanone,
1-(4-benzyloxypirrolidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone,
1-[4-(4-chlorobenzyloxy)-piperidine-1-yl)]-1-(6-hydroxy-1H-indol-2-il)methanone,
6-hydroxy-1H-indole-2-carboxylic acid 4-phenylbuthylamide,
(4-benzylpiperidine-1-yl)-(6-hydroxy-1H-benzoimidazol-2-yl)-methanone and
(6-hydroxy-1H-benzoimidazol-2-yl)-[4-(4-methyl-benzyl)-piperidine-1-yl]-methanone.

The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) as active ingredient.

Furthermore objects of the present invention are the synthesis of compounds of formula (I), and the chemical and pharmaceutical manufacture of medicaments containing these compounds, as well as the method of treatments with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

The term "halogen" substituent - as defined earlier - denotes fluorine, chlorine, bromine or iodine atoms, preferably fluorine and chlorine atoms. The term C_1-C_4 alkyl group used in the present description denotes methyl, ethyl, normal- and isopropyl and different butyl groups. These C_1-C_4 alkyl groups can be in the C_1-C_4 alkoxy groups. The term C_1-C_6 alkanoyloxy group denotes a monovalent acyloxy group consisting of a hydrogen

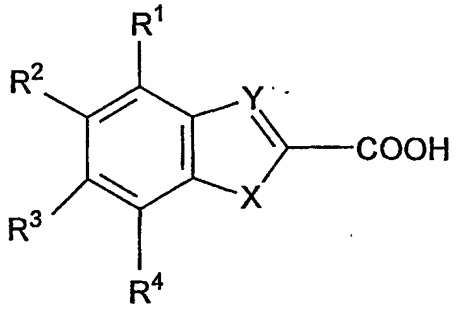
atom, as well as a C_1-C_6 alkyl group and a carbonyloxy group (-CO-O-) attached to it, preferably a formyloxy, an acetoxy, a propionyloxy, different butiryloxy, valeroyloxy and caproyloxy groups.

The invention relates also to the salts of compounds of formula (I) formed with acids or bases.

Both organic and inorganic acids can be used for the formation of acid addition salts. Suitable inorganic acids can be for example hydrochloric acid, sulfuric acid and phosphoric acid. Representatives of monovalent organic acids can be for example formic acid, acetic acid, propionic acid, and different butyric acids, valeric acids and capric acids. Representatives of bivalent organic acids can be for example oxalic acid, malonic acid, maleic acid, fumaric acid and succinic acid. Other organic acids can also be used, such as hydroxy acids for example citric acid, tartaric acid, or aromatic carboxylic acids for example benzoic acid or salicylic acid, as well as aliphatic and aromatic sulfonic acids for example methanesulfonic acid and p-toluenesulfonic acid. Especially valuable group of the acid addition salts is in which the acid component itself does not have therapeutical effect in the applied dose or it does not have unfavorable influence on the effect of the active ingredient. These acid addition salts are pharmaceutically acceptable acid addition salts. The reason why acid addition salts, which do not belong to the pharmaceutically acceptable acid addition salts belong to the present invention is, that in given case they can be advantageous in the purification and isolation of the desired compounds.

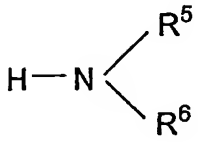
Among the salts formed with bases especially important are the salts formed with alkali metals, for example sodium, potassium, alkaline-earth metals, for example calcium and magnesium, as well as with ammonia or organic amines. The latter bases can have further substituents, for example hydroxy or amino groups, which can influence e.g. the solubility and the handling of the product.

According to the invention the compounds of formula (I) are synthesized by forming an amide bond between a carboxylic acid of formula (II)



(II)

- wherein the meaning of R^1, R^2, R^3, R^4, X and Y are as described before for the formula of (I) – and an amine of formula (III)



(III)

wherein the meaning of R^5 and R^6 are as given before for the formula of (I),

then the so obtained carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, R^3, R^4, R^5, R^6, X and Y is as defined for the formula of (I) – in given case is transformed into another compound of formula (I) by introducing new substituents and/or modifying or removing the existing ones, and/or salt formation and/or liberating the compound from salts, and/or the obtained racemates are resolved using optical active acids or bases by known methods.

The amide bond formation is preferably carried out by preparing an active derivative from a carboxylic acid of formula (II) and this is reacted with an amine of formula (III) preferably in the presence of a base.

The amide bond formation can be carried out either in solution or on solid phase with a carboxylic acid of formula (II).

In solution the transformation of a carboxylic acid into an active derivative is carried out *in situ* during the amide bond formation in a proper solvent (for example dimethylformamide, acetonitrile, chlorinated hydrocarbons or hydrocarbons). The active derivatives can be acid chlorides (for example prepared from carboxylic acid with thionyl chloride),

mixed anhydrides (for example prepared from carboxylic acid with isobutyl chloroformate in the presence of a base, e.g. triethylamine), active esters (for example prepared from carboxylic acid with hydroxybenztriazol and dicyclohexyl-carbodiimide or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) in the presence of a base e.g. triethylamine). The active derivatives are prepared between room temperature and 0 °C. To the so obtained solution or suspension a proper amine of formula (III) is added as base or as a salt formed with inorganic acid so that base, for example triethylamine, needed for the liberation of the amine is added to the reaction mixture separately. The condensation reactions are followed by thin layer chromatography. The necessary reaction time is 6-20 h. The work-up of the reaction mixture can be carried out by different methods.

When the reaction mixture is a suspension, the precipitate is filtered off and recrystallized from a proper solvent to give the pure product. If the crystallization does not lead to the pure product, then column chromatography can be used for the purification of it. The column chromatography is carried out either on normal phase using Kieselgel 60 as adsorbent and different solvent systems, e.g. toluene/methanol, chloroform/methanol or toluene/acetone, as eluents, or on reverse phase using Prep-Pak-500/C18 type packings (produced by Waters Associates) and acetonitrile/water/trifluoroacetic acid as eluent. If the reaction mixture is a solution at the end of the acylation, it is concentrated, and the residue is crystallized or purified by column chromatography as described above. The structures of the products are determined by IR, NMR and mass spectrometry.

Alternatively, the reaction mixture can be purified by column chromatography without concentration at the end of the reaction. The fractions having the desired compound are concentrated, the residue is dissolved in dimethylsulfoxide and the structure, the purity as well as the concentration of the product is determined by HPLC/MS (high pressure column chromatography, followed by mass spectrometry).

The carboxylic acid amide derivatives of formula (I) can be prepared on solid supports as follows: under an inert gas the properly substituted ester of a carboxylic acid of formula (II) is stirred in dimethylformamide in the presence of sodium methoxide at 70-80 °C with Merrifield resin. The excess of the reactants is washed out from the resin with different solvents, then the ester of carboxylic acid of formula (II) anchored onto the resin is

transformed into the carboxylic acid of formula (II) anchored onto the resin with potassium trimethylsilanolate in refluxing tetrahydrofuran. Then the excess of the reactants is again washed out from the resin with appropriate solvents. The carboxylic acid of formula (II) anchored onto the resin is transformed into an active ester with HBTU in dimethyl formamide and an amine of formula (III) in dimethyl formamide is added to the mixture. The mixture is shaken for example on a shaker until the end of the amidation reaction. The product is a carboxylic acid amide derivative of formula (I) anchored onto the resin. The carboxylic acid amide derivative of formula (I) is cleaved from the resin for example with a mixture of trifluoroacetic acid/dichloromethane.

The obtained carboxylic acid amide derivatives of formula (I) – independently from the method of preparation – in given case can be transformed into an other compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (I) can be transformed into a salt by treatment with a base.

For example cleaving the methyl and benzyl groups from methoxy and benzyloxy groups, which stands for R^1-R^4, leads to phenol derivatives. The removal of benzyl group can be carried out for example with catalytic hydrogenation or with hydrogen bromide in acetic acid solution, the cleavage of methyl group can be carried out with boron tribromide in dichloromethane solution. The compounds of formula (I) containing free phenolic hydroxy group can be transformed into acyloxy or sulfoxy derivatives with different acylating or sulfonylating agents. The reactions are carried out at room temperature in chlorinated hydrocarbons using acid chloride or acid anhydride as acylating agent in the presence of a base (for example triethylamine or sodium carbonate). The carboxylic acid amide derivatives of formula (I) containing a nitro group (I) can be transformed into amines by catalytic hydrogenation and the amines can be further reacted to give acid amides as described for the acylation of phenolic hydroxy groups. Free hydroxy groups can be esterified by acid anhydrides or acid halogenides in the presence of a base.

The carboxylic acids of formula (II) and the primary or secondary amines of formula (III) are either commercially available or can be synthesized by different known methods. The syntheses of some commercially not available carboxylic acid of formula (II) are described in the Examples. Following these procedures the other commercially not available carboxylic acids of formula (II) can also be prepared.

The compounds of the invention as well as their pharmaceutically acceptable salts can be used as such or suitably in the form of pharmaceutical compositions. These compositions (drugs) can be in solid, liquid or semiliquid form and pharmaceutical adjuvant and auxiliary materials can be added, which are commonly used in practice, such as carriers, excipients, diluents, stabilizers, wetting or emulsifying agents, pH- and osmotic pressure-influencing, flavoring or aromatizing, as well as formulation-promoting or formulation-providing additives.

The dosage required to exert the therapeutical effect can vary within wide limits and will be fitted to the individual requirements in each of the particular cases, depending on the stage of the disease, the condition and the bodyweight of the patient to be treated, as well as the sensitivity of the patient against the active ingredient, route of administration and number of daily treatments. The actual dose of the active ingredient to be used can safely be determined by the attending physician skilled in the art in the knowledge of the patient to be treated.

The pharmaceutical compositions containing the active ingredient according to the present invention usually contain 0.01 to 100 mg of active ingredient in a single dosage unit. It is, of course possible that the amount of the active ingredient in some compositions exceeds the upper or lower limits defined above.

The solid forms of the pharmaceutical compositions can be for example tablets, dragées, capsules, pills or lyophilized powder ampoules useful for the preparation of injections. Liquid compositions are the injectable and infusable compositions, fluid medicines, packing fluids and drops. Semiliquid compositions can be ointments, balsams, creams, shaking mixtures and suppositories.

For the sake of a simple administration it is suitable if the pharmaceutical compositions comprise dosage units containing the amount of the active ingredient to be adminis-

tered once, or a few multiples or a half, third or fourth part thereof. Such dosage units are e.g. tablets, which can be powdered with grooves promoting the halving or quartering of the tablet in order to exactly administer the required amount of the active ingredient.

Tablets can be coated with an acid-soluble layer in order to assure the release of the active ingredient content after leaving the stomach. Such tablets are enteric-coated. A similar effect can be achieved also by encapsulating the active ingredient.

The pharmaceutical compositions for oral administration can contain e.g. lactose or starch as excipients, sodium carboxymethylcellulose, methylcellulose, polyvinyl pyrrolidine or starch paste as binders or granulating agents. Potato starch or microcrystalline cellulose is added as disintegration agents, but ultraamylopectin or formaldehyde casein can also be used. Talcum, colloidic silicic acid, stearin, calcium or magnesium stearate can be used as antiadhesive and lubricants.

The tablet can be manufactured for example by wet granulation, followed by pressing. The mixed active ingredients and excipients, as well as in given case part of the disintegrants are granulated with an aqueous, alcoholic or aqueous alcoholic solution of the binders in an appropriate equipment, then the granulate is dried. The other disintegrants, lubricants and antiadhesive agents are added to the dried granulate, and the mixture is pressed to a tablet. In given case the tablets are made with halving groove to ease the administration.

The tablets can be made directly from the mixture of the active ingredient and the proper auxiliaries by pressing. In given case, the tablets can be coated by using additives commonly used in the pharmaceutical practice, for example stabilizers, flavoring, coloring agents, such as sugar, cellulose derivatives (methyl- or ethylcellulose, sodium carboxymethylcellulose, etc), polyvinyl pyrrolidone, calcium phosphate, calcium carbonate, food coloring agents, food laces, aroma agents, iron oxide pigments, etc. In the case of capsules the mixture of the active ingredient and the auxiliaries is filled into capsules.

Liquid oral compositions, for example suspensions, syrups, elixirs can be made by using water, glycols, oils, alcohols, coloring and flavoring agents.

For rectal administration the composition is formulated in suppositories or clysters. The suppository can contain beside the active ingredient a carrier, so called adeps pro sup-

pository. Carriers can be vegetable oils, such as hydrogenated vegetable oils, triglycerides of C_{12}-C_{18} fatty acids (preferably the carriers under the trade name Witepsol). The active ingredient is homogeneously mixed with the melted adeps pro suppository and the suppositories are moulded.

For parenteral administration the composition is formulated as injection solution. For manufacturing the injection solution the active ingredients are dissolved in distilled water and/or in different organic solvents, such as glycolethers, in given case in the presence of solubilizers, for example polioxyethylensorbitane-monolaurate, -monooleate, or monostearate (Tween 20, Tween 60, Tween 80). The injection solution can also contain different auxiliaries, such as conserving agents, for example ethylendiamine tetraacetate, as well as pH adjusting agents and buffers and in given case local anaesthetic, e.g. lidocain. The injection solution containing the active ingredient of the invention is filtered before it is filled into ampoules, and it is sterilized after filling.

If the active ingredient is hygroscopic, then it can be stabilized by liophylization.

Close structure analogs of the carboxylic acid amide derivatives of formula (I) are known from the literature.

Substituted indole-2-yl-carbonyl-piperidine derivatives, similar to the compounds of the invention, are described in patent No. WO 9618628 and two publications [J. Med. Chem., 39, 3769. (1996), and J. Med. Chem., 42, 4140. (1999)]. These compounds having revers transcriptase inhibiting effect can be used for treatment of AIDS patients.

Indole-2-carboxylic acid amides are also known [Bioorg. Med. Chem. Letters, 10, 483. (2000)] to inhibit $pp60^{c\text{-}src}$ tyrosine kinase, and therefore they can play a role in treatment of tumor patients. The publication does not describe NMDA receptor antagonist effect.

Benzofuran-2-yl-piperidine derivatives are described in patent No. WO 2000012074. These compounds have p38-a kinase inhibiting effect, and therefore can be used for treatment of infections caused by gram-negative bacteria as well as of patients suffering from respiratory distress syndrome.

A methanone derivative described in Protein Sci., 6(7), 1412. (1997) have thrombin inhibiting effect. The publication does not describe NMDA receptor antagonist effect.

Surprisingly it was found, that in contrast to the known, structurally analogous compounds - which are known to have only different enzyme inhibiting effects - the new carboxylic acid amide derivatives of formula (I) of the present invention are highly effective and selective antagonists of NMDA (N-methyl-D-aspartate) receptors, and moreover most of the compounds are selective antagonist of NR2B subtype of NMDA receptor. This selectivity is particularly important, as the undesired side effects of the compounds are less pronounced.

Antagonists of the NMDA receptors can be used in many disorders that are accompanied with excess release of glutamate, the main excitatory neurotransmitter in the central nervous system. Overactivation of NMDA receptors by glutamate can lead to calcium overload of the cells. This can trigger cascade of intracellular events that can alter the cell function and can lead even to death of neurons [TINS, **10**, 299-302 (1987)].

Our knowledge of NMDA receptor structure, function and pharmacology has expanded owing to recent achievements of molecular biology. The NMDA receptors are heteromeric assemblies built up from at least one NR1 subunit and at least one of the four NR2 subunits (NR2A-D). Both spatial distributions in CNS and pharmacological sensitivity of NMDA receptors built up from various NR2 subunits are different. Particularly interesting of these is NR2B subunit, because of its restricted distribution (highest density is in forebrain and substantia gelatinosa of spinal cord). Compounds selective for this subtype are available [Curr. Pharm. Des. **5**, 381-404 (1999)] and were proven to be effective in animal models of stroke [Stroke **28**, 2244-2251 (1997)], traumatic brain injury [Brain Res. **792**, 291-298 (1998)], Parkinson's disease [Exp. Neurol. **163**, 239-243 (2000)], neuropathic and inflammatory pain [Neuropharmacology **38**, 611-623 (1999)]. Subtype selective antagonists of NMDA receptors are expected to exhibit little or no untoward side effects caused by non-selective antagonists of NMDA receptors acting at glutamate binding site or within the channel pore.

Disorders known to be responsible to NMDA antagonists [Drug News Perspect **11**, 523-569 (1998) and WO 00/00197 international patent application] are cerebral ischemia of any origin (e.g. stroke, heart surgery), chronic neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's

disease, human immunodeficiency virus (HIV) related neuronal injury, traumatic injury of brain or spinal cord, pain (e.g. posttraumatic or postoperative) and chronic pain states, such as neuropathic pain or cancer related pain. NMDA receptor antagonists may also be used in epilepsy, anxiety, depression, migraine, psychosis, muscular spasm, multiinfarct dementia and in dementia of other origin, hypoglycemia, degenerative disorders of the retina (e.g. CMV retinitis) asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss. An NMDA antagonist can be useful to decrease tolerance and/or dependence to opioid treatment of pain, and for treatment of withdrawal syndrome of e.g. alcohol, opioids, and cocaine.

As the target compounds have the above mentioned biological effects, objects of the present invention are also the process of treatments with carboxylic acid amide derivatives of formula (I), or with the salts thereof, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

It is known that during postnatal development the subunit composition of neuronal NMDA receptors is changing. Similar change was detected in neuronal cell cultures [Eur. J. Neurosci. **10**, 1704-1715 (1998)]. According to literature data and to our own immunocitochemical examinations neuronal cells cultured for 4-7 days *in vitro* predominantly express the NR2B subunit, together with NR1 subunit. So functional test of NMDA antagonism in these cells mostly reflects action on NR2B subunit containing receptors. Since NMDA receptors are known to be permeable to calcium ions upon excitation, we characterized the NMDA receptor activation by measurement of rise in intracellular calcium concentration following the agonist (NMDA) application to the cells.

Assessment of NMDA antagonist potency *in vitro* by measurement of intracellular calcium concentration with a plate reader fluorimeter

The intracellular calcium measurements were carried out on primary neocortical cell cultures derived from 17 day old Charles River rat embryos (for the details on the preparation of neocortical cell culture see Johnson, M.I.; Bunge, R.P. (1992): Primary cell cultures of peripheral and central neurons and glia. In: Protocols for Neural Cell Culture, eds: Fedoroff, S.; Richardson A., The Humana Press Inc., 13-38.) After isolation the cells

were plated onto standard 96-well microplates and the cultures were maintained in an atmosphere of 95% air-5% CO_2 at 37 °C until the calcium measurements.

The cultures were used for the intracellular calcium measurements after 4-7 days in vitro. Before the measurement the cells were loaded with a fluorescent Ca^{2+}-sensitive dye, Fluo-4/AM (2-2.5 μM). To stop the loading the cells were washed twice with the solution used for the measurement (140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 5 mM HEPES, 5 mM HEPES-Na, 20 mM glucose, 10 μM glycine, pH=7.4). After washing the test compounds were added to the cells in the above solution (90 μl/well). Intracellular calcium measurements were carried out with a plate reader fluorimeter: elevation of Fluo-4-fluorescence and so, intracellular calcium was induced by application of 40 μM NMDA. Inhibitory potency of the test compounds was assessed by measuring the reduction in the calcium elevation in the presence of different concentrations of the compounds. After the measurement a standard calibration procedure with slight modifications was used to convert the fluorescent data to calcium concentration values [Meth. Cell. Biol. **40**, 155-181 (1994)].

Dose-response curves and IC_{50}-values were calculated by using data derived from at least three independent experiments. Inhibitory potency of a compound at a single concentration point was expressed as percent inhibition of the NMDA response. Sigmoidal concentration-inhibition curves were fit to the data and IC_{50} values were determined as the concentration that produces half of the maximal inhibition caused by the compound.

In Table 1 IC_{50} values for the most effective compounds of this invention measured in this test are listed (column 1-2) together with most effective reference compounds examined (column 3-4).

Table 1

Code number of compound	NMDA IC_{50} [μM]	Code of reference compound	NMDA IC_{50} [μM]
4570001103	0.0022	Co-101244	0.023
45 14216	0.004	EMD 95885	0.035
45 14071	0.007	CP 101,606	0.041
4570001378	0.009	Co-111103	0.060
45 13768	0.016	Ro 25.6981	0.159
45 70001033	0.016	ifenprodil	0.483
45 13579	0.018		
45 13754	0.024		
45 70001032	0.028		
45 14323	0.031		
45 14135	0.036		
45 14079	0.037		
45 14048	0.067		
45 14045	0.079		
45 13848	0.090		
45 13826	0.107		
45 13977	0.110		
45 70001036	0.114		
45 13846	0.136		
45 14217	0.163		
45 14132	0.180		
45 13869	0.186		

The reference compounds are as follows:

Co 101244: 1-[2-(4-hydroxyphenoxy)ethyl]-4-hydroxy-4-(4-methylbenzyl)piperidine

EMD 95885: 6-[3-(4-fluorobenzyl)piperidine-1-yl]propionyl]-2,3-dihydro-benzoxazol-2-on

CP-101,606: (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidine-1-yl)-1-propanol

Co-111103: 1-[2-(4-hydroxyphenoxy)ethyl]-4-(4-fluorobenzyl)piperidine

Ro 256981: R-(R*,S*)-1-(4-hydroxyphenyl)-2-methyl-3-[4-(phenylmethyl)piperidin-1-yl]-1-propanol.

As Table 1 shows, many of the compounds of this invention exceeds the potency of the known reference compounds examined by us.

Testing subunit selectivity on cells expressing recombinant rat NMDA receptors

In order to prove NR2B subunit selectivity of the compounds, cells transfected with cDNAs of the rat NR1a and NR2A or NR2B subunits were used. Genes cloned according to published sequences [gi508809 (rat NR1a), gi205738 (rat NR2B), gi2905805 (rat NR2A)] were inserted into inducible mammalian expression vectors bearing different resistance genes (hygromycine in the case of NR1a or neomycine in the case of NR2 subunits). The vector constructs were introduced into HEK293 cells using a cationic lipid-mediated transfection method. Protein expression was induced by 3 μM MuristeronA. Cells were maintained in the presence of 365 μM ketamine for 48-72 hours under an atmosphere of 95% air-5% CO_2 at 37 °C before the experiments.

Assessment of NMDA antagonist potency on cells transfected with NR1a/NR2B subunits-fluorimetric method

For establishment of cell clones stably expressing NR1a/NR2B receptors, transfected cells were exposed to the selecting antibiotics for 4 weeks then resistant clones were grown up. The expression of NR2B subunit protein was verified by a flow cytometry based immunocytochemical method. Positive clones were further tested for functional activity in patch clamp experiments. The best clone producing the highest NMDA evoked ion-current was used for testing NMDA antagonism by measuring NMDA induced elevation of cytosolic calcium concentration. Induction of protein expression and maintenance of cells was the same as described above.

The cells were plated onto standard 96-well microplates. A plate reader-based fluorometric assay was used to measure NMDA antagonism. The method was essentially similar to that described above for testing primary cultures of rat cortical neurons.

Assessment of NMDA antagonist potency on cells transfected with NR1a/NR2A subunits – patch clamp method

Cells transiently expressing NR1a/NR2A receptors and grown onto coverslips were used in patch clamp experiments. Whole-cell patch clamp recording was done according to the standard technique. Cell cultures were constantly superfused with an extracellular solution (140 mM NaCl, 5 mM KCl, 5 mM Hepes, 5 mM Na-Hepes, 2 mM CaCl2, 20 mM glucose, 10 μM glycine, pH 7.35) at room temperature. Patch pipettes with resistance between 3 and 6 MΩ were filled with an intracellular solution (140 mM CsCl, 11 mM EGTA, and 10 mM Hepes, pH 7.3). The inward current elicited by 100 μM NMDA was recorded from cells voltage clamped at -70 mV. Compounds were applied via a multibarrel ejection device controlled by electromagnetic valves. First NMDA was repeatedly administered until stabilization of the responses, then it was given in the presence of the test compound. The degree of inhibition – expressed as percentage – was calculated from the peak currents evoked by NMDA in the presence and absence of the test compound. Selectivity ratio (NR2B/NR2A), was calculated as the ratio of test dose on NR1/2A transfected cells and IC50 value of NMDA antagonism on NR1/NR2B expressing cells.

The results are given in Table 2.

Table 2

Assessment of selectivity for NR2B vs. NR2A subunit containing receptors

Compound	NR1/NR2B*	NR1/NR2A**		Selectivity
	IC_{50}	% Inhibition of NMDA current		
	[μM]	1 μM	40 μM	
45 13579	0.020		3	>2000
45 70001103	0.0011	21		>900
CP-101.606	0.033		2	>1200

*: Data obtained on HEK293 cells stably expressing NR1a/NR2B subunits by measurement of intracellular calcium concentration with a plate reader fluorimeter. Means of 3 experiments are given.

**: results of patch clamp experiments on NR1a/NR2A transiently transfected HEK cells. Test concentration was as indicated. Means of 3, 6, 2 experiments aare given for 45 13579, 450700011030 and CP-101,606, respectively.

Selectivity: selectivity ratio (NR2B/NR2A), calculated as ratio of test concentration on NR1/2A transfected cells and IC_{50} value on NR1/NR2B expressing cells.

According to the results in Table 2, compounds 45 13579 and 45 70001103 as well as CP-101,606 are highly selective toward NR2B subunit containing NMDA receptors.

The synthesis of compounds and pharmaceutical compositions according to the invention is illustrated by the following not limiting Examples. The code numbers of the compounds, which are referred in the biological tests, are given after the name of the compounds prepared in the Examples.

Example 1

1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (45 13579)

A mixture of 5.0 g (28.2 mmol) of 6-hydroxy-indole-2-carboxylic acid [J. Chem. Soc. 1605-1608. (1948)], 4.4 ml (31.6 mmol) of triethylamine, 5.0 g (28.5 mmol) of 4-benzylpiperidine, 12.0 g (31.6 mmol) of HBTU (Advanced Chem. Tech.) and 50 ml of dimethylformamide is stirred at room temperature for 6 h. The precipitated product is filtered off and recrystallized from ethanol to yield 6.75 g (71 %) of the title compound. Mp: 214-215 °C (ethanol).

Example 2

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-phenyl-3,6-dihydro-2H-pyridine-1-yl)methanone (45 13753)

A mixture of 0.8 g (4.5 mmol) of 6-hydroxy-indole-2-carboxylic acid, 20 ml of acetonitrile, 1.4 ml (10.06 mmol) of triethylamine, 0.9 g (4.6 mmol) of 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride and 1.8 g (4.75 mmol) of HBTU is stirred at room temperature for 6 h. The precipitated product is filtered off, and recrystallized twice from 90 % aqueous ethanol to yield 0.22 g (15.0 %) of the title compound. Mp.: 216-217 °C (ethanol)

Example 3

1-(4-Benzylpiperidine-1-yl)-1-(5-hydroxy-1H-indole-2-yl)methanone (45 13754)

A mixture of 0.8 g (4.5 mmol) of 5-hydroxy-indole-2-carboxylic acid, 0.7 ml (5.0 mmol) of triethylamin, 0.9 g (5.1 mmol) of 4-benzylpiperidine, 1.8 g (4.75 mmol) of HBTU and 15 ml of acetonitrile is stirred at room temperature for 6 h. The reaction mixture is concentrated and the residue is purified by column chromatography using Kieselgel 60 as adsorbent (Merck) and toluene : methanol = 4 : 1 as eluent, then the product is recrystallized from isopropanol to yield 0.47 g (31 %) of the title compound. Mp.: 199 °C (isopropanol).

Example 4

1-(4-Benzyloxypiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (45 13768)

The title compound is prepared from 4-benzyloxypiperidin [Tetrahedron 54, 13981. (1998)] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 2. Mp.: 203-204 °C (isopropanol)

Example 5

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-phenylaminopiperidine-1-yl)methanone (45 13794)

The title compound is prepared from 4-phenylaminopiperide [Chem. Pharm. Bull. 33, 1826. (1985)] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 213 °C (ethanol).

Example 6

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-phenylethylpiperidine-1-yl)methanone (45 13795)

The title compound is prepared from 4-phenylethylpiperidine [J. Org. Chem. **22,** 1376. (1957)] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 157-159 °C (ethanol)

Example 7

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-phenylpiperidine-1-yl)methanone (45 13796)

The title compound is prepared from 4-phenylpiperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 105 °C (isopropanol).

Example 8

1-[4-Hydroxy-4-(4-chlorophenyl)piperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone

(45 13824)

The title compound is prepared from 4-hydroxy-4-(4-chlorophenyl)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 220 °C (isopropanol).

Example 9

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-phenoxypiperidine)methanone (45 13826)

The title compound is prepared from 4-phenoxypiperidine [US 3260723] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 155-156 °C (isopropanol).

Example 10

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-phenoxy-3,6-dihydro-2H-pyridine-1-yl)methanone (45 13846)

A mixture of 1.0 g (5.64 mmol) of 6-hydroxy-indole-2-carboxylic acid 0.8 ml (5.7 mmol) of triethylamin, 1.04g (5.8 mmol) of 4-phenoxy-3,6-dihydro-2H-pyridine [Chem. Ber., 48, 960. (1915.)], 2.14 g (5.64 mmol) of HBTU and 15 ml of dimethyl-formamide is stirred at room temperature for 6 h. The reaction mixture is concentrated and the residue is purified by column chromatography using Kieselgel 60 as adsorbent (Merck) and toluene : methanol = 4 : 1 as eluent, then the product is recrystallized from isopropanol to yield 1.13 g (59.6 %) of the title compound. Mp.: 102-103 °C (isopropanol)

Example 11

1-(4-Benzylaminopiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (45 13847)

The title compound is prepared from 4-benzylaminopiperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 220 °C (isopropanol).

Example 12

1-[4-(4-Fluorobenzyl)piperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone (45 13848)

The title compound is prepared from 4-(4-fluorobenzyl)piperidine [J. Med. Chem., 35, 4903. (1992)] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 180-182 °C (toluene).

Example 13

1-(4-Benzylpiperidine-1-yl)-1-[6-hydroxy-7-(piperidine-1-yl-methyl)-1H-indole-2-yl]methanone (45 13880)

A solution of 0.7 g (2.09 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone in 20 ml of a 4 : 1 mixture of dioxane : acetic acid is refluxed in the presence of 0.22 ml (2.00 mmol) of piperidine and 0.07 g (2.33 mmol) of paraformaldehyde for 2 h. The reaction mixture is concentrated and the residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. The product is isolated as hydrochloride salt using an isopropanolic solution of hydrogen chloride and diethyl ether. Yield: 0.11 g (12 %). Mp.: 134 °C (diethyl ether – isopropanol).

Example 14

1-[4-(4-Fluorobenzyl)-4-hydroxypiperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone (45 13906)

The title compound is prepared from 4-(4-fluorobenzyl)-4-hydroxypiperidine [J. Pharm. Pharmacol., 18, 150. (1966)] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 222 °C (isopropanol).

Example 15

1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxy-5-methoxy-1H-indole-2-yl)methanone (45 13941)

a) 6-Hydroxy-5-methoxy-1H-indole-2-carboxylic acid

A mixture of 7.4 g (24.9 mmol) of 6-benzyloxy-5-methoxy-1H-indole-2-carboxylic acid [J. Het. Chem., 2, 387. (1965)], 100 ml of methanol and 0.5 g of 10 % Pd/C catalyst is hydrogenated for 0.5 h. The catalyst is filtered off, the filtrate is concentrated and the residue is recrystallized from isopropanol to yield 3.75 g (38 %) of the title compound. Mp.: 245-247 °C (isopropanol).

b) 1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxy-5-methoxy-1H-indole-2-yl)methanone

The title compound is prepared from 4-benzylpiperidine and 6-hydroxy-5-methoxy-1H-indole-2-carboxylic acid according to the method described in Example 1. Mp.: 150 °C (isopropanol).

Example 16

1-(4-Benzylpiperidine-1-yl)-1-(5-hydroxy-6-methoxy-1H-indole-2-yl)methanone (45 13946)

a) 5-Hydroxy-6-methoxy-1H-indole-2-carboxylic acid

A mixture of 5.32 g (17.9 mmol) of 5-benzyloxy-6-methoxy-1H-indole-2-carboxylic acid [J. Het. Chem., 2, 387. (1965)], 100 ml of methanol and 0.2 g of 10 % Pd/C catalyst is hydrogenated for 0.5 h. The catalyst is filtered off, the filtrate is concentrated and the residue is recrystallized from isopropanol to yield 2.37 g (53 %) of the title compound. Mp.: 212 °C (isopropanol).

b) 1-(4-Benzylpiperidine-1-yl)-1-(5-hydroxy-6-methoxy-1H-indole-2-yl)methanone

The title compound is prepared from 4-benzylpiperidine and 5-hydroxy-6-methoxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 196 °C (isopropanol)

Example 17

1-(6-Benzyloxy-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (45 13971)

The title compound is prepared from 4-benzylpiperidine and 6-benzyloxy-1H-indole-2-carboxylic acid [J. Chem. Soc., 1605. (1948)] according to the method described in Example 1. Mp.: 182 °C (ethanol).

Example 18

1-(4-Benzylpiperidine-1-yl)-1-(4,6-dimethoxy-1H-indole-2-yl)methanone (45 13972)

The title compound is prepared from 4-benzylpiperidine and 4,6-dimethoxy-1H-indole-2-carboxylic acid according to the method described in Example 1. Mp.: 224 °C (ethanol).

Example 19

1-(4-Benzoylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (45 13975)

The title compound is prepared from 4-benzoylpiperidine [DE 2708913] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10.Mp.: 190-191 °C (toluene - methanol).

Example 20

1-[4-(1-Hydroxy-1,1-diphenylmethyl)piperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone (45 14001)

The title compound is prepared from azacyclonol (α,α-diphenyl-4-piperidinyl-methanol) and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 3. Mp.: 134-135 °C (toluene).

Example 21

Ethyl 2-{1-[1-(6-hydroxy-1H-indole-2-yl)methanoyl]piperidine-4-yl-methoxy}benzoate

(45 14044)

The title compound is prepared from ethyl 2-(piperidine-4-yl-methoxy)benzoate and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 182 °C (ethanol).

Example 22

1-(6-Acetoxy-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (45 14045)

To a stirred mixture of 0.5 g (1.5 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (Example 1) and 0.24 ml (1.7 mmol) of triethylamin in 20 ml of dichloromethane 0.12 ml (1.7 mmol) of acetyl chloride in 5 ml of dichloromethane is added. The reaction mixture is stirred at room temperature for 1 h, then washed with water, the organic layer is concentrated and the residue is recrystallized from ethanol to yield 0.35 g (62 %) of the title compound. Mp.: 159 °C (ethanol).

Example 23

1-(4-Benzylpiperidine-1-yl)-1-(7-hydroxy-6-methoxy-1H-indole-2-yl)methanone (45 14046)

a) Methyl (Z)-2-azido-3-(3-benzyloxy-4-methoxyphenyl)acrylate

Under argon, to a sodium methoxide solution (prepared from 3.8 g (165 mmol) of sodium and 90 ml of methanol) a mixture of 10.0 g (41.2 mmol) of 3-benzyloxy-4-methoxybenzaldehyde and 19.0 g (165 mmol) of methyl azidoacetate in 40 ml of methanol is added at 0 °C. The mixture is stirred at 0 °C for 4 h, then diluted with 300 ml of water and extracted with chloroform. The organic layer is washed with water, dried over sodium sulfate, concentrated and the residue is crystallized with ethanol to yield 9.0 g (64 %) of the title compound. Mp.: 108 °C (ethanol).

b) Methyl 7-benzyloxy-6-methoxy-indole-2-carboxylate

To a stirred solution of 300 ml of boiling xylene 9.0 g (26.5 mmol) of methyl (Z)-2-azido-3-(3-benzyloxy-4-methoxyphenyl)acrylate is added in small portions. After completion of the addition the reaction mixture is refluxed until the gas formation is over (about 0.5 h), then cooled to room temperature, the precipitated product is filtered off and recrystallized from isopropanol. The so obtained product is methyl 5-benzyloxy-6-methoxy-indole-2-carboxylate [yield: 5.44g (66%)]. Mp.: 189 °C.

The mother liquor is concentrated and the residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and hexane – ethyl acetate = 4:1 as eluent to give methyl 7-benzyloxy-6-methoxy-indole-2-carboxylate. Yield: 1.8 g oil (22%).

c) 7-Benzyloxy-6-methoxy-indole-2-carboxylic acid

The title compound is prepared from methyl 7-benzyloxy-6-methoxy-indole-2-carboxylate according to the method described in Example 25/a. Mp.: 135-137 °C (water).

d) 1-(4-Benzylpiperidine-1-yl)-1-(7-benzyloxy-6-methoxy-1H-indole-2-yl)methanone

The title compound is prepared from 7-benzyloxy-6-methoxy-indole-2-carboxylic acid and 4-benzylpiperidine according to the method described in Example 10. Mp.: 107-108 °C (isopropanol).

e) 1-(4-Benzylpiperidine-1-yl)-1-(7-hydroxy-6-methoxy-1H-indole-2-yl)methanone

A mixture of 0.52g (1.14 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(7-benzyloxy-6-methoxy-1H-indole-2-yl)methanone, 20 ml of methanol and 0.03 g of 10 % Pd/C catalyst is hydrogenated for 2 h. The catalyst is filtered off, the filtrate is concentrated and the residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene - acetone = 1 : 1 as eluent, then the product is recrystallized from isopropanol to yield 0.32 g (77 %) of the title compound. Mp.: 186-187 °C (isopropanol).

Example 24

1-[6-(2-Aminoethoxy)-1H-indole-2-yl]-1-(4-benzylpiperidine-1-yl)methanone (45 14047)

a) 1-[6-(2-*tert*-Butoxycarbonylaminoethoxy)-1H-indole-2-yl]-1-(4-benzylpiperidine-1-yl)metha-none

To a solution of 1.0 g (2.99 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone and 20 ml of dimethylformamide 1.0 g (4.46 mmol) of *tert*-butyl (2-bromoethyl)carbamate and 1.0 g (7.24 mmol) of potassium carbonate are added, and the mixture is stirred at 80-90 °C for 10 h. The reaction mixture is filtered, the filtrate is concentrated, and the residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and chloroform : methanol = 10 : 1 as eluent to yield 0.8 g of the title compound as oil.

b) 1-[6-(Aminoethoxy)-1H-indole-2-yl]-1-(4-benzylpiperidine-1-yl)methanone

To a solution of 0.8 g (1.67 mmol) of 1-[6-(2-*tert*-butoxycarbonylamino-ethoxy)-1H-indole-2-yl]-1-(4-benzylpiperidine-1-yl)methanone and 10 ml of dichloromethan 10 ml of 10 % trifluoroacetic acid solution in dichloromethane is added and the mixture is stirred at room temperature for 6 h. Then the reaction mixture is concentrated and the residue is crystallized with isopropanol. The product is transformed into base form with 2 M sodium hydroxide solution, extracted with chloroform, the organic layer is concentrated and the residue is crystallized with isopropanol to yield 75 mg (12 %) of the title compound. Mp.: 166 °C (isopropanol).

Example 25

1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxy-7-methoxy-1H-indole-2-yl)methanone (45 14048)

a) 6-Benzyloxy-7-methoxy-1H-indole-2-carboxylic acid

A mixture of 1.22 g (3.92 mmol) of methyl 6-benzyloxy-7-methoxy-indole-2-carboxylate and 0.75 g (5.84 mmol) of potassium trimethylsilanolate in 50 ml of tetrahydrofuran is refluxed for 1 h. Then the reaction mixture is cooled, poured into 100 ml of water and acidified with hydrochloric acid. The precipitated product is filtered off, washed with water and dried to yield 1.13 g (97 %) of the title compound. Mp: 230-231 °C (water).

b) 1-(4-Benzylpiperidine-1-yl)-1-(6-benzyloxy-7-methoxy-1H-indole-2-yl)methanone

The title compound is prepared from 6-benzyloxy-7-methoxy-1H-indole-2-carboxylic acid and 4-benzylpiperidine according to the method described in Example 10. Mp.: 124-125 °C (isopropanol).

c) 1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxy-7-methoxy-1H-indole-2-yl)methanone

The title compound is prepared from 1-(4-benzylpiperidine-1-yl)-1-(6-benzyloxy-7-methoxy-1H-indole-2-yl)methanone according to the method described in Example 23/e. Mp.: 230-231 °C (methanol).

Example 26

1-(4-Benzylpiperidine-1-yl)-(4,6-dihydroxy-1H-indole-2-yl)methanone (45 14071)

a) Methyl (Z)-2-azido-3-(2,4-dibenzyloxy)acrylate

The title compound is prepared from 2,4-dibenzyloxybenzaldehyde according to the method described in Example 23/a. Mp.: 174 °C (ethanol).

b) Methyl 4,6-dibenzyloxy-1H-indole-2-carboxylate

The title compound is prepared from methyl (Z)-2-azido-3-(2,4-dibenzyloxy)acrylate according to the method described in Example 23/b. Mp.: 180 °C (isopropanol).

c) 4,6-Dibenzyloxy-1H-indole-2-carboxylic acid

The title compound is prepared from methyl 4,6-dibenzyloxy-1H-indole-2-carboxylate according to the method described in Example 15. Mp: 180 °C (water).

d) 1-(4-Benzylpiperidine-1-yl)-1-(4,6-dibenzyloxy-1H-indole-2-yl)methanone

The title compound is prepared as an oil from 4,6-dibenzyloxy-1H-indole-2-carboxylic acid and 4-benzylpiperidine according to the method described in Example 10.

e) 1-(4-Benzylpiperidine-1-yl)-1-(4,6-dihydroxy-1H-indole-2-yl)methanone

The title compound is prepared from 1-(4-benzylpiperidine-1-yl)-1-(4,6-dibenzyloxy-1H-indole-2-yl)methanone according to the method described in Example 23/e. Mp.: 245-246 °C (isopropanol).

Example 27

1-(4-Benzhydrylidenepiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (45 14073)

A mixture of 2.0 g (4.69 mmol) of 1-[4-(1-hydroxy-1,1-diphenylmethyl)piperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone (Example 20) and 15 ml of trifluoroacetic acid is stirred at room temperature for 1 h. The product is precipitated with water and re-crystallized from isopropanol to yield 1.4 g (73 %) of the title compound. Mp.: 166-167 °C (isopropanol).

Example 28

1-[4-(4-Chlorobenzyloxy)-1-(6-hydroxy-1H-indole-2-yl)piperidine-1-yl]methanone (45 14132)

The title compound is prepared from 4-(4-chlorobenzyloxy)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 167-168 °C (toluene – methanol).

Example 29

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-phenoxymethylpiperidine-1-yl)methanone (45 14135)

The title compound is prepared from 4-phenoxymethylpiperidine [Synth. Commun., 17, 1815. (1987)] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 104 °C (isopropanol).

Example 30

1-(4-Benzylpiperidine-1-yl)-1-(5,6-dihydroxy-1H-indole-2-yl)methanone (45 14136)

a) 1-(4-Benzylpiperidine-1-yl)-1-(5,6-dibenzyloxy-1H-indole-2-yl)methanone

The title compound is prepared from 5,6-dibenzyloxy-1H-indol-2-carboxylic acid [J. Het. Chem., 2, 387. (1965)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 207 °C (toluene – methanol).

b) 1-(4-Benzylpiperidine-1-yl)-1-(5,6-dibenzyloxy-1H-indole-2-yl)methanone

The title compound is prepared from 1-(4-benzylpiperidine-1-yl)-1-(5,6-dibenzyloxy-1H-indole-2-yl)methanone according to the method described in Example 23/e. Mp.: 208-209 °C (ethyl acetate).

Example 31

1-(3-Benzyloxypiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (45 14163)

The title compound is prepared from 3-benzyloxypiperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 170 °C (isopropanol).

Example 32

1-(4-Benzylpiperidin-1-yl)-1-(6-methanesulfonyloxy-1H-indole-2-yl)methanone (45 14164)

To a stirred solution of 0.5 g (1.5 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (Example 1) and 0.24 ml (1.7 mmol) of triethylamine in 20 ml of dichloromethane 0.12 ml (1.55 mmol) of methansulfonyl chloride in 5 ml of dichloromethane is added. The reaction mixture is stirred at room temperature for 1 h, then washed with water and the organic layer is concentrated. The residue is recrystallized from ethanol to yield 0.4 g (65 %) of the title compound. Mp.: 199-200 °C (ethanol).

Example 33

1-(6-Hydroxy-1H-indole-2-yl)-1-[2-(4-methoxybenzyl)-piperidine-1-yl]methanone (45 14189)

To a mixture of 15 mg (0.0847 mmol) of 6-hydroxy-indole-2-carboxylic acid, 0.25 ml of dimethylformamide, 0.026 ml (0.0847 mmol) of triethylamine and 20.5 mg (0.0847 mmol) of 2-(4-methoxybenzyl)piperidine hydrochloride 35 mg (0.0847 mmol) of HBTU in 0.25 ml of dimethylformamide is added. The reaction mixture is stirred at room temperature for 6 h, then concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : methanol = 4 : 1 as eluent. The quality and the quantity of the product are determined by HPLC-MS method, on a Discovery C16 Amide column using 0,1 % of trifluoroacetic acid in aqueous acetonitril as eluent and electrospray ionization. R_f = 0.33 (toluene – methanol = 4 : 1)

Example 34

1-(6-Hydroxy-1H-indole-2-yl)-1-[3-(2-methoxybenzyl)piperidine-1-yl]methanone (45 14190)

The title compound is prepared from 3-(2-methoxybenzyl)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 35

1-(6-Hydroxy-1H-indole-2-yl)-1-{2-[1-hydroxy-1-(3-methoxyphenyl)methyl]piperidine-1-yl}methanone (45 14191)

The title compound is prepared from 2-[1-hydroxy-1-(3-methoxyphenyl)methyl]-piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 36

1-[3-(3,4-Dimethoxybenzyl)piperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone (45 14192)

The title compound is prepared from 3-(3,4-dimethoxybenzyl)-piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 37

1-(6-Hydroxy-1H-indole-2-yl)-1-[3-(3,4,5-trimethoxybenzyl)piperidine-1-yl]methanone

(45 14193)

The title compound is prepared from 3-(3,4,5-trimethoxybenzyl)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 38

1-(4-Benzyloxypiperidine-1-yl)-1-(4,6-dihydroxy-1H-indole-2-yl)methanone (45 14216)

The title compound is prepared from 4-benzyloxypiperidine and 4,6-dihydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 178-179 °C (toluene – methanol).

Example 39

1-(4-Benzyloxypyrrolidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (45 14217)

The title compound is prepared from 4-benzyloxypyrrolidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 184-185 °C (isopropanol).

Example 40

1-(6-Hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyl)-piperidine-1-yl]methanone (45 14221)

The title compound is prepared from 4-(4-methylbenzyl)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 10. Mp.: 164 °C (isopropanol).

Example 41

1-(4-Benzylpiperidine-1-yl)-1-(6-pivaloyloxy-1H-indole-2-yl)methanone (45 14247)

To a stirred mixture of 0.5 g (1.5 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone (Example 1), 20 ml of dichloromethane and 0.24 ml (1.7 mmol) of triethylamine 0.2 ml (1.6 mmol) of pivaloyl chloride in 5 ml of dichlo-

romethane is added. The reaction mixture is stirred at room temperature for 1 h, then washed with water, the organic layer is concentrated and the residue is recrystallized from ethanol to yield 0.08 g (8 %) of the title compound. Mp.: 236-238 °C (ethanol).

Example 42

1-(4-Benzylpiperidine-1-yl)-1-(5,7-dihydroxy-1H-indole-2-yl)methanone (45 14323)

a) Methyl (Z)-2-azido-3-(3,5-dibenzyloxy)acrylate

The title compound is prepared from 3,5-dibenzyloxybenzaldehyde according to the method described in Example 23/a. Mp.: 107-108 °C (ethanol).

b) Methyl 5,7-dibenzyloxy-1H-indole-2-carboxylate

The title compound is prepared from methyl (Z)-2-azido-3-(3,5-dibenzyloxy)acrylate according to the method described in Example 23/b. Mp.: 143-144 °C (isopropanol).

c) 5,7-Dibenzyloxy-1H-indole-2-carboxylic acid

The title compound is prepared from methyl 5,7-dibenzyloxy-1H-indole-2-carboxylate according to the method described in Example 25/a. Mp: 191 °C (water).

d) 1-(4-Benzylpiperidine-1-yl)-1-(5,7-dibenzyloxy-1H-indole-2-yl)methanone

The title compound is prepared from 5,7-dibenzyloxy-1H-indole-2-carboxylic acid and 4-benzylpiperidine according to the method described in Example 1. The crude product is used in the next step.

e) 1-(4-Benzylpiperidine-1-yl)-1-(5,7-dihydroxy-1H-indole-2-yl)methanone

The title compound is prepared from 1-(4-benzylpiperidine-1-yl)-1-(5,7-dibenzyloxy-1H-indole-2-yl)methanone according to the method described in Example 23/e. Mp.: 198 °C (toluene – methanol).

Example 43

1-(6-Hydroxy-1H-indole-2-yl)-1-[3-(4-methoxybenzyl)piperidine-1-yl])methanone (45 7000 1026)

The title compound is prepared from 3-(4-methoxybenzyl)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 44

1-[4-(2-Ethoxyphenoxy)piperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone (45 70001027)

The title compound is prepared from 4-(2-ethoxyphenoxy)piperidine and 6-hydroxy-1H-indole-2-carboxylic according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1).

Example 45

1-(6-Hydroxy-1H-indole-2-yl)-1-[3-(4-isobutoxybenzyl)piperidine-1-yl]methanone (45 7000 1029)

The title compound is prepared from 3-(4-isobutoxybenzyl)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 46

6-Hydroxy-1H-indole-2-carboxylic acid (4-phenylcyclohexyl)amide (45 7000 1030)

The title compound is prepared from 4-phenylcyclohexylamine [J. Org. Chem., 1017. (1952)] and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 47

1-[3-(2-Ethoxyphenoxymethyl)piperidine-1-yl]-1-(6-hydroxy-1H-indole-2-yl)methanone (45 7000 1031)

The title compound is prepared from 3-(2-ethoxyphenoxymethyl)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 48

1-(6-Hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyloxy)piperidine-1-yl]methanone (45 7000 1032)

The title compound is prepared from 4-(4-methylbenzyloxy)piperidine and 6-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.33 (toluene - methanol = 4 : 1)

Example 49

1-(4-Benzylpiperidine-1-yl)-1-(4-hydroxy-1H-indole-2-yl)methanone (45 7000 1033)

The title compound is prepared from 4-benzylpiperidine and 4-hydroxy-1H-indole-2-carboxylic acid [J. Med. Chem., **34**, 1283. (1991)] according to the method described in Example 33. R_f = 0.4 (toluene - methanol = 4 : 1)

Example 50

1-(4-Benzyloxypiperidine-1-yl)-1-(4-hydroxy-1H-indole-2-yl)methanone (45 7000 1034)

The title compound is prepared from 4-benzyloxypiperidine and 4-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.4 (toluene - methanol = 4 : 1)

Example 51

1-(4-Hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyloxy)piperidine-1-yl]methanone (45 7000 1035)

The title compound is prepared from 4-(4-methylbenzylyoxy)piperidine and 4-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.4 (toluene - methanol = 4 : 1)

Example 52

1-(4-Hydroxy-1H-indole-2-yl)-1-(4-phenoxymethylpiperidine-1-yl)methanone (45 7000 1036)

The title compound is prepared from 4-phenoxymethylpiperidine and 4-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.4 (toluene - methanol = 4 : 1)

Example 53

1-(4-Hydroxy-1H-indole-2-yl)-1-[4-(1-phenyletoxy)piperidine-1-yl]methanone (45 7000 1037)

The title compound is prepared from 4-(1-phenylethoxy)piperidine and 4-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.4 (toluene – methanol = 4 : 1)

Example 54

1-(4-Hydroxy-1H-indole-2-yl)-1-(4-phenoxypiperidine-1-yl)methanone (45 7000 1038)

The title compound is prepared from 4-phenoxypiperidine and 4-hydroxy-1H-indole-2-carboxylic acid according to the method described in Example 33. R_f = 0.4 (toluene - methanol = 4 : 1)

Example 55

1-(4-Benzylpiperidine-1-yl)-1-(5-hydroxybenzofuran-2-yl)methanone (45 13830)

The title compound is prepared from 5-hydroxybenzofuran-2-carboxylic acid [Helv. Chim. Acta 77, 100. (1994)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 148-153 °C (diethylether).

Example 56

1-(5-Hydroxybenzofuran-2-yl)-1-(4-phenylpiperidine-1-yl)methanone (45 13860)

The title compound is prepared from 5-hydroxybenzofuran-2-carboxylic acid and 4-phenylpiperidine according to the method described in Example 10. Mp.: 160-162 °C (diethylether).

Example 57

1-(5-Hydroxybenzofuran-2-yl)-1-(4-phenyl-4-hydroxypiperidine-1-yl)methanone (45 13861)

The title compound is prepared from 5-hydroxybenzofuran-2-carboxylic acid and 4-phenyl-4-hydroxypiperidine according to the method described in Example 10. Mp.: 188-192 °C (diethylether).

Example 58

1-(4-Benzyloxypiperidine-1-yl)-1-(5-hydroxybenzofuran-2-yl)methanone (45 13862)

The title compound is prepared from 5-hydroxybenzofuran-2-carboxylic acid and 4-benzyloxypiperidine according to the method described in Example 10. Mp.: 148-152 °C (diethylether).

Example 59

1-(4-Benzylpiperidine-1-yl)-1-(6-methoxybenzofuran-2-yl)methanone (45 13952)

The title compound is prepared from 6-methoxybenzofuran-2-carboxylic acid [J. Chem. Soc., 787. (1940)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 88-90 °C (diethylether).

Example 60

1-(4-Benzyloxypiperidine-1-yl)-1-(5-hydroxy-1H-indole-2-yl)methanone (45 13953)

The title compound is prepared from 5-hydroxyindole-2-carboxylic acid and 4-benzyloxypiperidine according to the method described in Example 10. Mp.: 184-186 °C (diethylether).

Example 61

1-[4-(4-Fluorobenzyl)piperidine-1-yl]-1-(5-hydroxy-1H-indole-2-yl)methanone (45 13977)

The title compound is prepared from 5-hydroxyindole-2-carboxylic acid and 4-(4-fluorobenzyl)piperidine according to the method described in Example 10. Mp.: 204-206 °C (diethylether).

Example 62

1-(5-Hydroxy-1H-indole-2-yl)-1-(4-phenoxy-3,6-dihydro-2H-pyridine-1-yl)methanone (45 13994)

The title compound is prepared from 5-hydroxyindole-2-carboxylic acid and 4-phenoxy-1,2,3,6-tetrahydropyridine according to the method described in Example 10. Mp.: 153-155 °C (diethylether).

Example 63

1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxybenzofuran-2-yl)methanone (45 13995)

The title compound is prepared from 6-hydroxybenzofuran-2-carboxylic acid [J. Chem. Soc., 2254. (1948)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 183-186 °C (diethylether).

Example 64

1-(4-Benzyloxypiperidine-1-yl)-1-(6-hydroxybenzofuran-2-yl)methanone (45 13997)

The title compound is prepared from 6-hydroxybenzofuran-2-carboxylic acid and 4-benzyloxypiperidine according to the method described in Example 10. Mp.: 144-146 °C (diethylether).

Example 65

1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxybenzothiazole-2-yl)methanone (45 14055)

a) Methyl 6-methoxybenzothiazole-2-carboxylate

To a stirred solution of 8.3 g (40 mmol) of 6-methoxybenzothiazole-2-carboxylic acid [J. Am. Chem. Soc., **85**, 337. (1963)] in 80 ml of methanol 4.8 ml of thionyl chloride is added at 0 °C, then the reaction mixture is stirred at room temperature for 10 h. The precipitated crystals are filtered off, washed with methanol to yield 6.0 g (67 %) of the title compound. Mp.: 130-135 °C (methanol).

b) Methyl 6-hydroxybenzothiazole-2-carboxylate

To a stirred solution of 6.0 g (27 mmol) of methyl 6-methoxybenzothiazole-2-carboxylate in 60 ml of dichloromethane 2.6 ml of boron tribromide in 10 ml of dichloromethane is added dropwise at –15 °C. The reaction mixture is stirred at room temperature for 10 h, then poured into ice-water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and hexane – ethyl acetate = 2 : 1 as eluent to yield 2.0 g (36 %) of the title compound. Mp.: 200-206 °C (hexane – ethyl acetate).

c) 6-Hydroxybenzothiazole-2-carboxylic acid

A stirred mixture of 2.0 g of methyl 6-hydroxybenzothiazole-2-carboxylate (9.6 mmol), 100 ml of ethanol and 1.1 g of potassium hydroxide is refluxed for 1 h. The reaction mixture is cooled to 10 °C, the precipitated crystals are filtered off, washed with ethanol, dissolved in water and acidified with 20 % aqueous sulfuric acid. The precipitated crystals are filtered off and washed with water to yield 1.85 g (99 %) of the title compound. Mp.: 128-132 °C (water).

d) 1-(4-Benzylpiperidine-1-yl)-1-(6-hydroxybenzothiazole-2-yl)methanone

The title compound is prepared from 6-hydroxybenzothiazole-2-carboxylic acid and 4-benzylpiperidine according to the method described in Example 10. Mp.: 68-70 °C (diethylether).

Example 66

1-(4-Benzyloxypiperidine-1-yl)-1-(6-hydroxybenzothiazole-2-yl)methanone (45 14056)

The title compound is prepared from 6-hydroxybenzothiazole-2-carboxylic acid and 4-benzyloxypiperidine according to the method described in Example 10. Mp.: 166-172 °C (diethylether).

Example 67

1-(4-Benzylpiperidine-1-yl)-1-(5-nitrobenzofuran-2-yl)methanone (45 14159)

The title compound is prepared from 5-nitrobenzofuran-2-carboxylic acid [Helv. Chim. Acta 31, 75. (1948)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 123-125 °C (diethylether).

Example 68

1-(4-Benzylpiperidine-1-yl)-1-(6-methoxybenzothiazole-2-yl)methanone (45 14160)

The title compound is prepared from 6-methoxybenzothiazole-2-carboxylic acid and 4-benzylpiperidine according to the method described in Example 10. Mp.: 107-109 °C (diethylether).

Example 69

1-(5-Aminobenzofuran-2-yl)-1-(4-benzylpiperidine-1-yl)methanone hydrochloride (45 14208)

A stirred mixture of 2.0 g (5.5 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(5-nitrobenzofuran-2-yl)methanone (Example 67), 100 ml of tetrahydrofuran and 0.2 g of 10 % Pd/C is hydrogenated. After completion of the reaction, the catalyst is filtered off, washed with tetrahydrofuran and the filtrate is concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : acetone = 4 : 1 as eluent to yield 1.8 g (98 %) of the title compound as oil.

1 g of the so obtained oil is dissolved in isopropanol and acidified with hydrogen chloride in diethylether (pH=1). The precipitated crystals are filtered off and washed with diethylether to yield 0.72 g (65 %) of the title compound. Mp.: 246-250 °C (diethylether – isopropanol).

Example 70

1-(5-Acetylaminobenzofuran-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (45 14207)

A mixture of 330 mg (1 mmol) of 1-(5-aminobenzofuran-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (Example 69), 6 ml of pyridine and 3 ml of acetic anhydride is stirred at room temperature for 2 h, then poured into ice-water. The precipitated crystals are filtered off and washed with water to yield 280 mg (78 %) of the title compound. Mp.: 179-184 °C (pyridine - water).

Example 71

1-(5-Hydroxy-1H-indole-2-yl)-1-(4-phenoxypiperidine-1-yl]methanone (45 14209)

The title compound is prepared from 5-hydroxyindole-2-carboxylic acid and 4-phenoxypiperidine according to the method described Example 10. Mp.: 155-158 °C (di-ethylether).

Example 72

1-(4-Benzylpiperidine-1-yl)-1-(5-methanesulfonylaminobenzofuran-2-yl)methanone (45 14120)

A mixture of 330 mg (1 mmol) of 1-(5-aminobenzofuran-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (Example 69), 6 ml of pyridine and 0.5 ml of methane-sulfonyl chloride is stirred at room temperature for 2 h, then poured into ice-water. The product is extracted with dichloromethane, the combined organic layers are washed with 5 % ice-cold aqueous sulfuric acid, water, 5 % aqueous sodium hydrogencarbonate solution, then again with water, dried over sodium sulfate and concentrated. The residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and toluene : acetone = 4 : 1 as eluent to yield 280 mg (69 %) of the title compound. Mp.: 155-158 °C (hexane).

Example 73

6-[1-(4-Benzylpiperidin-1-yl)methanoyl]-3H-furo[2,3-f]benzoxazol-2-on (45 14255)

a) Ethyl 3H-furo[2,3-f]benzoxazol-2-on-6-carboxylate

A mixture of 0.9 g (4.2 mmol) of ethyl 5-hydroxy-6-aminobenzofuran-2-carboxylate [Helv. Chim. Acta 77, 100. (1994)], 60 ml of tetrahydrofuran, 3.1 ml of 20 % phosgene in toluene solution and 2.0 ml of triethylamine is stirred at room temperature for 1 h. The tetrahydrofuran is distilled off in vacuum, water is added to the residue and the product is extracted with ethyl acetate. The combined organic layers are washed with 5 % aqueous sodium hydrogencarbonate solution, water, 1 N hydrochloric acid solution and again with water, dried over sodium sulfate and concentrated to yield 1.0 g (96 %) of the title compound as oil.

b) 3H-Furo[2,3-f]benzoxazol-2-on-6-carboxylic acid

A stirred mixture of 1.0 g (4 mmol) of ethyl 3H-furo[2,3-f]benzoxazol-2-on-6-carboxylate, 100 ml of ethanol and 0.5 g of potassium hydroxide is refluxed for 1 h. The mixture is concentrated, the residue is dissolved in water and acidified with 20 % aqueous

sulfuric acid solution. The precipitated crystals are filtered off and washed with water to yield 0.84 g (95 %) of the title compound. Mp.: 190-192 °C (water).

c) 6-[1-(4-Benzylpiperidine-1-yl)methanoyl]-3H-furo[2,3-f]benzoxazol-2-on

The title compound is prepared from 3H-furo[2,3-f]benzoxazol-2-on-6-carboxylic acid and 4-benzylpiperidine according to the method described in Example 10. Mp.: 123-125 °C (diethylether).

Example 74

6-[1-(4-Benzyloxypiperidine-1-yl)methanoyl]-3H-furo[2,3-f]benzoxazol-2-on (45 14254)

The title compound is prepared from 3H-furo[2,3-f]benzoxazol-2-on-6-carboxylic acid and 4-benzyloxypiperidine according to the method described in Example 10. Mp.: 217-219 °C (diethylether).

Example 75

1-(4-Benzylpiperidine-1-yl)-1-(5-methoxybenzothiophene-2-yl)methanone (45 13936)

The title compound is prepared from 5-methoxybenzothiophene-2-carboxylic acid [J. Org. Chem., 26, 1326. (1961)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 128-130 °C (diethylether).

Example 76

1-(4-Benzylpiperidine-1-yl)-1-(5-hydroxybenzothiophene-2-yl)methanone (45 13951)

To a solution of 0.68 g (1.9 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(5-methoxybenzothiophene-2-yl)methanone (Example 75) in 10 ml of dichloromethane 4 ml of 1 M boron tribromide in dichloromethane is added dropwise at -20 °C, the reaction mixture is stirred at room temperature for 10 h, then concentrated. The residue is stirred with 20 ml of 5 % aqueous sodium hydrogencarbonate solution, the precipitated crystals are filtered off and washed with water to yield 0.63 g (94 %) of the title compound. Mp.: 162 °C (decomposing) (water).

Example 77

1-(4-Benzylpiperidine-1-yl)-1-(5-methoxybenzothiophene-1,1'-dioxide-2-yl)methanone (45 14243)

To a suspension of 0.72 g (2 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(5-methoxybenzothiophene-2-yl)methanone (Example 75) in 50 ml of methanol 3.2 ml (50 mmol) of 30 % hydrogen peroxide solution and 0.08 g (0.8 mmol) of selenium dioxide are added, and the mixture is stirred at room temperature for 10 h. Then an additional amount, the same as before, of hydrogen peroxide and selenium dioxide are added, and the reaction mixture is stirred for a further 5 h. This operation is repeated twice more. Finally the mixture is concentrated and the residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and chloroform as eluent to yield 0.26 g (33 %) of the title compound. Mp.: 147-149 °C (diethylether).

Example 78

1-(6-Hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyl)-4-hydroxypiperidine-1-yl]methanone (45 14079)

The title compound is prepared from 6-hydroxyindole-2-carboxylic acid and 4-(4-methylbenzyl)-4-hydroxypiperidine [J. Med. Chem., 42, 2993. (1999)] according to the method described in Example 10. Mp.: 136-141 °C (diethylether).

Example 79

1-(5-Hydroxy-1H-indole-2-yl)-1-[4-(4-metylbenzyl)-4-hydroxypiperidine-1-yl]methanone (45 14308)

The title compound is prepared from 5-hydroxyindole-2-carboxylic acid and 4-(4-methylbenzyl)-4-hydroxypiperidine according to the method described in Example 10. Mp.: 226-229 °C (diethylether).

Example 80

1-(4-Benzylpiperidine-1-yl)-1-(5-hydroxynaphthalene-2-yl)methanone (45 14204)

The title compound is prepared from 5-hydroxy-2-naphthoic acid (Aldrich) and 4-benzylpiperidine according to the method described in Example 10. Mp.: 174-176 °C (diethylether).

Example 81

1-(4-Benzylpiperidine-1-yl)-1-(5-sulfonamidoindole-2-yl)methanone (45 14222)

The title compound is prepared from 5-sulfonamidoindole-2-carboxylic acid [Ann. Chim. (Rome), 51, 663. (1961)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 176-179 °C (diethylether).

Example 82

1-(6-Hydroxy-1H-indole-2-yl)-1-(4-hydroxypiperidine-1-yl)methanone (45 14 276)

The title compound is prepared from 6-hydroxyindole-2-carboxylic acid and 4-hydroxypiperidine according to the method described in Example 10. Mp.: 243-247 °C (diethylether).

Example 83

1-(5-Hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyl)-3,6-dihydro-2H-pyridine-1-yl]methanone (45 14309)

The title compound is prepared from 5-hydroxyindole-2-carboxylic acid and 4-(4-methylbenzyl)-1,2,3,6-tetrahydropyridine according to the method described in Example 10 using chloroform : methanol = 9 : 1 as eluent. Mp.: 224-226 °C (diethylether).

Example 84

1-(4-Benzylpiperidine-1-yl)-1-(5-nitro-1H-indole-2-yl)methanone (45 14205)

The title compound is prepared from 5-nitroindole-2-carboxylic acid (J. Am. Chem. Soc.; 4621 (1958)] and 4-benzylpiperidine according to the method described in Example 10. Mp.: 220-224 °C (diethylether).

Example 85

1-(5-Amino-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (45 14244)

A mixture of 0.5 g (1.38 mmol) of 1-(4-benzylpiperidine-1-yl)-1-(5-nitro-1H-indole-2-yl)methanone, 20 ml of methanol and 0.1 g of 10 % Pd/C catalyst is hydrogenated for 5 h. The catalyst is filtered off, washed with methanol and the filtrate is concentrated. The residue is treated with diethylether and the precipitated crystals are filtered off to yield 0.27 g (59 %) of the title compound. Mp.: 175-180 °C (diethylether).

Example 86

1-(5-Acetylamino-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (45 14310)

To a stirred solution of 0.5 g (1.5 mmol) of 1-(5-amino-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (Example 85) in 10 ml of chloroform 0.3 ml (3 mmol) of

acetic anhydride in 3 ml chloroform is added dropwise below 10 °C, then the mixture is stirred at room temperature for 10 h. The precipitated crystals are filtered off and washed with chloroform to yield 0.47 g (83 %) of the title compound. Mp.: 183-185 °C (chloroform).

Example 87

1-(4-Benzylpiperidine-1-yl)-1-(5-methanesulfonylamino-1H-indole-2-yl)methanone (45 14311)

To a stirred solution of 0.5 g (1.5 mmol) of 1-(5-amino-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (Example 85) and 0.42 ml of triethylamine in 10 ml of chloroform 0.25 ml (3 mmol) of methanesulfonyl chloride 3 ml of chloroform is added dropwise below 10 °C, and the reaction mixture is stirred at room temperature for 10 h. Then 30 ml of water is added to the mixture, the organic layer is separated and the water phase is extracted three times with 10 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated, the residue is treated with diethylether and the crystals are filtered to yield 0.5 g (81 %) of the title compound. Mp.: 111-114 °C (diethylether).

Example 88

1-(4-Benzylpiperidine-1-yl)-1-(5-trifluoroacetylamino-1H-indole-2-yl)methanone (45 7000 1020)

To a stirred solution of 0.5 g (1.5 mmol) of 1-(5-amino-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (Example 85) and 0.42 ml of triethylamine in 10 ml of chloroform 0.42 ml (3 mmol) of trifluoroacetic anhydride in 5 ml of chloroform is added dropwise below 10 °C, and the mixture is stirred at room temperature for 10 h. Then 30 ml of water and 30 ml of chloroform are added to the reaction mixture, the organic layer is separated and the water phase is extracted three times with 20 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated, the residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and [(butyl acetate : 25 % aqueous ammonia : water) = 1 : 1 : 1] : ethyl acetate = 1 : 19 as eluent. The product is crystallized with diethylether and filtered to yield 0.15 g (24 %) of the title compound. Mp.: 220-223 °C (diethylether).

Example 89

1-(4-Benzylpiperidine-1-yl)-1-(5-trifluoromethanesulfonylamino-1H-indole-2-yl)methanone (45 7000 1021)

To a stirred solution of 0.5 g (1.5 mmol) of 1-(5-amino-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone (Example 85) and 0.42 ml of triethylamine in 10 ml of chloroform 0.42 ml (3 mmol) of trifluoromethanesulfonic anhydride in 5 ml of chloroform is added dropwise below 10 °C, and the mixture is stirred at room temperature for 10 h. Then 100 ml of water and 100 ml of chloroform are added to the reaction mixture, the organic layer is separated and the water phase is extracted three times with 20 ml of chloroform. The combined organic layers are dried over sodium sulfate, concentrated, the residue is purified by column chromatography using Kieselgel 60 (Merck) as adsorbent and chloroform : methanol = 99 : 1 as eluent. The product is crystallized with diethylether and filtered to yield 0.045 g (6 %) of the title compound. Mp.: 215-219 °C (diethylether).

Example 90

1-(4-Benzylpiperidine-1-yl)-1-(5-chloro-1H-indole-2-yl)methanone (45 13985)

The title compound is prepared from 5-chloroindole-2-carboxylic acid (Aldrich) and 4-benzylpiperidine according to the method described in Example 10. Mp.: 182-183 °C (diethylether).

Example 91

1-(4-Benzylpiperidine-1-yl)-1-(5-fluoro-1H-indole-2-yl)methanone (45 13993)

The title compound is prepared from 5-fluoroindole-2-carboxylic acid (Aldrich) and 4-benzylpiperidine according to the method described in Example 10. Mp.: 177-180 °C (diethylether).

Example 92

1-(4-Benzylpiperidine-1-yl)-1-(1,6-dihydro-1,6-diaza-as-indacene-2-yl)methanone (45 14305)

a) Methyl (Z)-2-azido-3-(1H-indole-5-yl)acrylate

Under nitrogen, to a sodium methoxide solution (prepared from 15 ml of methanol and 0.66 g (29 mmol) of sodium) a mixture of 1.02 g (7 mmol) of indole-5-carbaldehyde [Helv. Chim. Acta, 1616. (1968)], 3.34 g (29 mmol) of methyl azido-acetate and 7 ml of

methanol is added dropwise at 0 °C and the so obtained mixture is stirred at this temperature for 5 h. Then the reaction mixture is diluted with 50 ml of water, and extracted three times with 50 ml of chloroform. The combined organic layers are washed with 20 ml of water, filtered through a phase separating filter-paper and concentrated to yield 1.3 g (77 %) of the title compound. Mp.: 130-133 °C (chloroform).

b) Methyl 1,6-dihydro-1,6-diaza-as-indacene-2-carboxylate

To a boiling solution of 36 ml of xylene 1.09 g (4.5 mmol) of methyl (Z)-2-azido-3-(1H-indole-5-yl)acrylate is added in small portions. The reaction mixture is refluxed till the end of the nitrogen gas formation, then concentrated and the residue is crystallized with hexane, the product is filtered and washed with hexane to yield 0.6 g (62 %) of the title compound. Mp.: 183-184 °C (hexane).

c) 1,6-Dihydro-1,6-diaza-as-indacene-2-carboxylic acid

A mixture of 0.53 g (2.5 mmol) of methyl 1,6-dihydro-1,6-diaza-as-indacene-2-carboxylate, 0.36 g (2.5 mmol) of potassium trimethylsilanolate (Aldrich) and 6.0 ml of tetrahydrofuran is refluxed for 1 h, further 0.18 g (1.25 mmol) of potassium trimethylsilanolate is added and after 5 h reflux the reaction mixture is concentrated. The residue is mixed with 20 ml of water, the undissolved material is filtered off, 0.32 ml of hydrochloric acid is added to the filtrate, the precipitated crude product is filtered off and purified by column chromatography using Kieselgel 60 (Merck) as adsorbent, and chloroform : methanol = 9 : 1 as eluent. The product is crystallized with diethylether to yield 0.22 g (44 %) of the title compound. Mp.: 248-250 °C (diethylether).

d) 1-(4-Benzylpiperidin-1-yl)-1-(1,6-dihydro-1,6-diaza-as-indacene-2-yl)methanone

The title compound is prepared from 1,6-dihydro-1,6-diaza-as-indacene-2-carboxylic acid and 4-benzylpiperidine according to the method described in Example 10. Mp.: 186-188 °C (diethylether).

Example 93

6-Hydroxy-1H-indole-2-carboxylic acid 4-phenylbutylamide (45 13869)

Method A. (synthesis in solution)

A mixture of 2.0 g (11.28 mmol) of 6-hydroxyindole-2-carboxylic acid, 4.24 g (11.28 mmol) of HBTU, 1.56 ml (11.28 mmol) of triethylamine and 40 ml of dimethyl-

formamide is stirred at room temperature for 15 min, then 1.68 g (11.28 mmol) of 4-phenylbutylamine is added. The reaction mixture is stirred at room temperature for 24 h and concentrated. The residue is dissolved in 100 ml of chloroform, washed three times with 30 ml of 8% aqueous sodium hydrogencarbonate solution, three times with 30 ml of 1 M hydrochloric acid, and three times with 30 ml of water. The organic layer is dried over sodium sulfate, concentrated and purified by column chromatography as follows. The obtained 3.02 g oil is dissolved in 5 ml of eluent (which is a 3 : 2 mixture of 60 % aqueous acetonitrile and 0.1 % aqueous trifluoroacetic acid) and submitted to column chromatography using Prep-Pak-500/C18 column and the above eluent. The fractions having the pure product are concentrated. The obtained residue is crystallized with acetonitrile to yield 1.28 g (34 %) of the title compound. Mp.: 82-83 °C (acetonitrile).

Method B. (solid phase synthesis)

a) Methyl 6-hydroxyindole-2-carboxylate anchored onto resin

A mixture of 50.0 g (62.5 mmol) of Merrifield resin (Bachem; capacity: 1,25 mM/g; size: 100-200 mesh), 375 ml of dimethylformamide, 35.81 g (187.5 mmol) of methyl 6-hydroxyindole-2-carboxylate is stirred for 20 min, then 10.2 g (188 mmol) of sodium methoxide is added. The reaction mixture is stirred at 70-77 °C under argon for 7 h, then the product is filtered off, washed twice with 300 ml of dimethylformamide, twice with 300 ml of tetrahydrofuran, twice with 300 ml of dimethylformamide and twice with 300 ml of tetrahydrofuran. The obtained product is stored wet until further use.

b) 6-hydroxyindole-2-carboxylic acid anchored onto resin

Under argon, to a mixture of methyl 6-hydroxyindole-2-carboxylate obtained in the previous step in 700 ml of tetrahydrofuran 40 g (312.5 mmol) of potassium trimethylsilanolate is added. The stirred reaction mixture is refluxed for 1 h 15 min, then filtered. The product is washed twice with 300 ml of dimethylformamide, twice with 300 ml of methanol, twice with 300 ml of dimethylformamide, twice with 300 ml of methanol, twice with 300 ml of dimethylformamide, finally again twice with 300 ml of methanol. The product is dried at room temperature to yield 58.7 g of the title compound.

c) 6-Hydroxy-1H-indole-2-carboxylic acid 4-phenylbutylamide anchored onto resin

To 0.3 g (0.31 mmol) of 6-hydroxyindole-2-carboxylic acid anchored onto resin 1.92 ml (0.96 mmol) of 0.5 M HBTU in dimethylformamide is added. It is shaken on an orbital shaker with 100 1/min rotations for 20 min, then 0.96 ml (0.96 mmol) of 1.0 M 4-phenylbutylamine in dimethylformamide is added. The reaction mixture is shaken on an orbital shaker with 100 1/min rotations for 6 h. Then the resin is filtered off and washed five times with 4 ml of dimethylformamide and three times with 4 ml of dichloromethane.

d) 6-Hydroxy-1H-indole-2-carboxylic acid 4-phenylbutylamide

A mixture of 0.31 mmol of 6-hydroxy-1H-indole-2-carboxylic acid 4-phenylbutylamide anchored onto resin and 2.1 ml of a 1 : 2 mixture of trifluoroacetic acid : dichloromethane is shaken on an orbital shaker with 100 1/min rotations for 2 h. Then the resin is filtered off and washed twice with 1.5 ml of dichloromethane. The combined filtrate is concentrated to yield the title compound. R_f=0.5 (60 % aqueous acetonitrile : 0.1 % aqueous trifluoroacetic acid = 3:2).

Example 94

6-Hydroxy-1H-indole-2-carboxylic acid 1,2-diphenylethylamide (45 13872)

The title compound is prepared from 6-hydroxyindole-2-carboxylic acid and 1,2-diphenylethylamine according to the methods A and B described in Example 93. Mp.: 97-98 °C (acetonitrile).

Example 95

6-Hydroxy-1H-indole-2-carboxylic acid 2-(4-bromophenyl)ethylamide (45 13870)

The title compound is prepared from 6-hydroxyindole-2-carboxylic acid and 2-(4-bromophenyl)ethylamine according to the methods A and B described in Example 93. Mp.: 192-195 °C (acetonitrile).

Example 96

6-Hydroxy-1H-indole-2-carboxylic acid 2-(4-chlorophenyl)ethylamide (45 13868)

The title compound is prepared from 6-hydroxyindole-2-carboxylic acid and 2-(4-chlorophenyl)ethylamine according to the methods A and B described in Example 93. Mp.: 205-207 °C (acetonitrile).

Example 97

6-Hydroxy-1H-indole-2-carboxylic acid 3-phenylpropylamide (45 13867)

The title compound is prepared from 6-hydroxyindole-2-carboxylic acid and 3-phenylpropylamine according to the methods A and B described in Example 93. Mp.: 155-157 °C (acetonitrile).

Example 98

5-Hydroxy-1H-indole-2-carboxylic acid 4-phenylbutylamide (45 14120)

The title compound is prepared from 5-hydroxyindole-2-carboxylic acid and 4-phenylbutylamine according to the methods A and B described in Example 93. Mp.: 164-166 °C (diethylether).

Example 99

6-Hydroxy-1H-indole-2-carboxylic acid 2-benzyloxyethylamide (45 14187)

The title compound is prepared from 6-hydroxyindole-2-carboxylic acid and 2-benzyloxyethylamine according to the methods A and B described in Example 93. Mp.: 142-143 °C (diethylether).

Example 100

(4-Benzylpiperidine-1-yl)-(6-hydroxy-1H-benzoimidazol-2-yl)-methanone (45 70001103)

a) N-Butyl-N′-(4-methoxy-2-nitro-phenyl)oxalamide

To a suspension of 44.0 g (164 mmol) of N-(4-methoxy-2-nitro-phenyl)oxalamic acid ethyl ester [J. Med. Chem., **18,** 926 (1975)] and 330 ml toluene 16.8 ml (170 mmol) of n-butylamin is added under 20 °C. The reaction mixture is stirred at room temperature for 10 h, then concentrated and the residue is crystallized with diethyl ether, the precipitated product is filtered off, washed with diethyl ether and dried to yield 45.3 g (93.3 %) of the title compound. Mp.: 127-128 °C (diethyl ether).

b) N-(2-Amino-4-methoxy-phenyl)-N′-butyl-oxalamide

A mixture of 27.0 g (91 mmol) of N-Butyl-N′-(4-methoxy-2-nitro-phenyl)oxalamide, 1200 ml of methanol and 7.3 g of 5% Pd/C catalyst is hydrogenated for 3 h. To the reaction mixture is added 600 ml of acetone. The catalyst is filtered off, washed with acetone, the filtrate is concentrated and the residue is crystallized with diethyl ether to yield 21.8 g (90.1 %) of the titled compound. Mp.: 180-181 °C (diethyl ether).

c) 6-Methoxy-1H-benzoimidazole-2-carboxylic acid butylamide

Under nitrogen, 41.0 g (154 mmol) of N-(2-amino-4-methoxy-phenyl)-N'-butil-oxalamide is stirred at 240 °C for 10 min. The mixture is cooled to room temperature then 300 ml of acetone is added, and stirred for 1 h. The precipitated product is filtered off. The filtrate is concentrated and the residue is mixed with 150 ml of n-hexane. The precipitated product is filtered off, washed with hexane and dried to yield 26.5 g (69.5 %) of the title compound. Mp.: 125-126 °C (n-hexane).

d) 6-Hydroxy-1H-benzoimidazole-2-carboxylic acid

A mixture of 26.0 g (105 mmol) of 6-methoxy-1H-benzoimidazole-2-carboxylic acid butilamide and 780 ml of 48 % aqueus hydrobromic acid is stirred at 110 °C for 8 h, then refluxed for 12 h. The mixture is cooled to room temperature, the precipitated product is filtered off, washed with water until pH neutral and dried to yield 14.3 g (76.2 %) of the title compound. Mp.: 206-207 °C (water).

e) (4-Benzylpiperidine-1-yl)-(6-hydroxy-1H-benzoimidazol-2-yl)-methanone (45 70001103)

A mixture of 3.0 g (16.75 mmol) of 6-hydroxi-1H-benzoimidazol-2-carboxilic acid, 2.4 ml (17.2 mmol) of triethylamin, 3.0 g (17.1 mmol) of 4-benzyl-piperidine, 7.0 g (18.5 mmol) of HBTU and 100 ml of dimethylformamide is stirred at room temperature for 16 h. The reaction mixture is concentrated and the residue is purified by coloumn chromatography using Kieselgel 60 as adsorbent (Merck) and toluene : methanol = 4 : 1 as eluent, then the product is recrystallized from toluene to yield 3.58 g (63.5 %) of the title compound. Mp.: 186 °C (toluene).

Example 101

(6-Hydroxy-1H-benzoimidazol-2-yl)-[4-(4-methyl-benzyl)-piperidine-1-yl]-methanone 45 70001378

The title compound is prepared from 6-hydroxy-1H-benzoimidazole-2-carboxylic acid [Example előző d] and 4-(4-methylbenzyl)piperidine [J.Org. Chem., 64, 3763 (1999)] according to the method described in Example 100. Mp.: 93 °C (diisopropyl ether).

Example 102

Preparation of pharmaceutical compositions:

a) Tablets:

0.01-50 % of active ingredient, 15-50 % of lactose, 15-50 % of potato starch, 5-15 % of polyvinyl pyrrolidone, 1-5 % of talc, 0.01-3 % of magnesium stearate, 1-3 % of colloid silicon dioxide and 2-7 % of ultraamylopectin are mixed, then are granulated by wet granulation and pressed to tablets.

b) Dragées, filmcoated tablets:

The tablets made according to the method described above are coated by a layer consisting of entero- or gastrosolvent film, or of sugar and talc. The dragées are polished by a mixture of beeswax and carnuba wax.

c) Capsules:

0.01-50 % of active ingredient, 1-5 % of sodium lauryl sulfate, 15-50 % of starch, 15-50 % of lactose, 1-3 % of colloid silicon dioxide and 0.01-3 % of magnesium stearate are thoroughly mixed, the mixture is passed through a sieve and filled in hard gelatin capsules.

d) Suspensions:

Ingredients: 0.01-15 % of active ingredient, 0.1-2 % of sodium hydroxide, 0.1-3 % of citric acid, 0.05-0.2 % of nipagin (sodium methyl 4-hydroxybenzoate), 0.005-0.02 % of nipasol, 0.01-0.5 % of carbopol (polyacrilic acid), 0.1-5 % of 96 % ethanol, 0.1-1 % of flavoring agent, 20-70 % of sorbitol (70 % aqueous solution) and 30-50 % of distilled water.

To solution of nipagin and citric acid in 20 ml of distilled water, carbopol is added in small portions under vigorous stirring, and the solution is left to stand for 10-12 h. Then the sodium hydroxide in 1 ml of distilled water, the aqueous solution of sorbitol and finally the ethanolic raspberry flavor are added with stirring. To this carrier the active ingredient is added in small portions and suspended with an immersing homogenizator. Finally the suspension is filled up to the desired final volume with distilled water and the suspension syrup is passed through a colloid milling equipment.

e) Suppositories:

For each suppository 0.01-15% of active ingredient and 1-20% of lactose are thoroughly mixed, then 50-95% of adeps pro suppository (for example Witepsol 4) is melted,

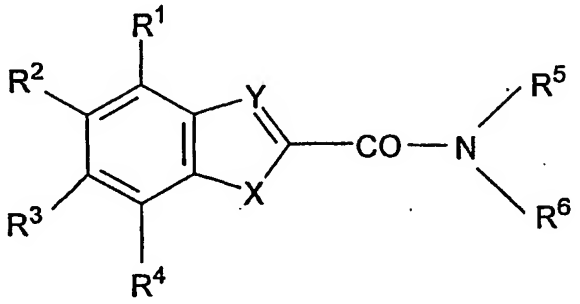
cooled to 35 °C and the mixture of active ingredient and lactose is mixed in it with homogenizator. The obtained mixture is mould in cooled forms.

f) Lyophilized powder ampoule compositions:

A 5 % solution of mannitol or lactose is made with bidistilled water for injection use, and the solution is filtered so as to have sterile solution. A 0.01-5 % solution of the active ingredient is also made with bidistilled water for injection use, and this solution is filtered so as to have sterile solution. These two solutions are mixed under aseptic conditions, filled in 1 ml portions into ampoules, the content of the ampoules is lyophilized, and the ampoules are sealed under nitrogen. The contents of the ampoules are dissolved in sterile water or 0.9 % (physiological) sterile aqueous sodium chloride solution before administration.

What we claim is:

1. New NMDA receptor antagonistic carboxylic acid amide derivatives of formula (I)



(I)

- wherein

R^1, R^2, R^3 and R^4 independently are hydrogen or halogen atom, hydroxyl, nitro, amino, carboxyl, sulfamoyl [NH_2-SO_2-], cyano, carbamoyl [-CO-NH_2], hydroxycarbamoyl [-CO-NHOH], thiocarbamoyl [-CS-NH_2], amidino [-C=(NH)-NH_2], hydroxyamidino [-C=(NOH)-NH_2], formyl [-CHO], hydroxyimino-methyl [-CH=NOH], amino-methyl [-CH_2-NH_2], hydroxymethyl, C_1-C_4 alkoxymethyl, halogenmethyl, tetrazolyl or imidazoline-2-yl group, or

C_1-C_4 alkoxy, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkanoyloxy, C_1-C_4 alkylsulfonamido – in given case substituted by a halogen atom or halogen atoms, C_1-C_4 alkanoylamido – in given case substituted by a halogen atom or halogen atoms, C_1-C_4 alkylsulfonyloxy, piperidyl-C_1-C_4 alkyl, phenyl or C_1-C_4 alkoxy groups, substituted by amino group, or

in given case benzoyloxy group substituted by halogen atom, C_1-C_4 alkyl, C_1-C_4 alkoxy or aliphatic or cyclic amino group, or

alkanoyloxy, alkanoyl-amido, benzamido, or benzenesulfonyl-amido group, substituted by aliphatic or cyclic amino group or

ureido [-NH-CO-NH_2] or thioureido group [-NH-CS-NH_2], substituted by C_1-C_4 alkyl or phenyl group or

in given case amidino group [-C(=NH)-NH_2], substituted on the primer amino by one or two C_1-C_4 alkyl group, wherein in given case the two C_1-C_4 alkyl groups together with the nitrogen atom between them can form a 5-7 membered heterocyclic ring, or

in given case ureidoimino-methyl [-CH=N-NH-CO-NH_2] or thioureidoimino-methyl group [-CH=N-NH-CS-NH_2], substituted by C_1-C_4 alkyl or phenyl group or

in given case aminoimino-methyl [-CH=N-NH_2] group substituted by a C_1-C_4 alkyl or phenyl group

with the restriction, that the meaning of at least one of R^1, R^2, R^3 and R^4 is different from hydrogen atom, and if the meaning of R^2 is amidino group, as well as the meaning of X is -NH- group, then the meaning of -$CONR^5R^6$ group is different from 4-benzyl-piperidino group, or

two of the neighboring R^1, R^2, R^3 and R^4 groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH_2- groups can form a 4-7 membered homo- or heterocyclic ring, preferably pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

from among R^5 and R^6 one of them is hydrogen atom and then the other is phenyl-cyclohexyl group or C_1-C_4 alkyl group, substituted by one or two hydroxy, phenyl, hydroxyphenyl or halogenphenyl groups, or

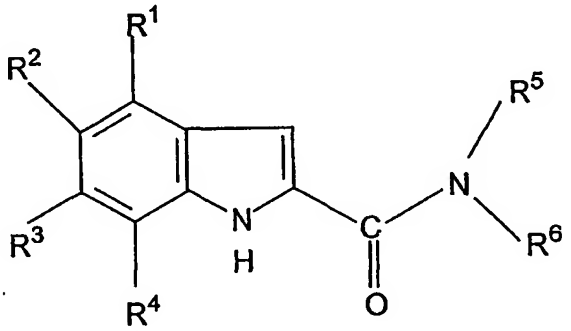
R^5 and R^6 together with the nitrogen between them form a saturated or unsaturated 4-6 membered heterocyclic ring, which is substituted by hydroxy group, and/or in given case phenyl or phenoxy, phenyl-(C_1-C_4 alkyl), phenyl-(C_1-C_4 alkoxy), phenoxy-(C_1-C_4 alkyl), anilino,

phenyl-(C_1-C_4 alkylamino), [phenyl-(C_1-C_4 alkyl)]-amino, benzoyl, hydroxy-diphenylmethyl, C_1-C_4 alkoxycarbonyl-phenoxymethyl or benzhydrylidene group, substituted on the aromatic ring by one or more halogen atom, cyano or hydroxy group, C_1-C_4 alkyl or C_1-C_4 alkoxy group,

the meaning of X and Y is independently oxygen, nitrogen or sulfur atom, as well as -CH=, -CH=CH-, -CH_2-, -SO-, -SO_2-, -NH- or -NR-group, wherein the meaning of R is hydrogen atom or C_1-C_4 alkyl group,

as well as the racemates, optical antipodes and the salts thereof formed with acids and bases.

2. Carboxylic acid amide derivatives of formula (Ia), which is a limited group of carboxylic acid amide derivatives of claim 1,



(Ia)

- wherein the meaning of R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in claim 1 – as well as the racemates, optical antipodes and the salts thereof formed with acids and bases.

3. One compound of the following group of carboxylic acid amide derivatives belonging to the scope of claim 1

1-(4-benzyloxypiperidine-1-yl)-1-(4,6-dihydroxy-1H-indole-2-yl)methanone,

1-(4-benzylpiperidine-1-yl)-1-(4,6-dihydroxy-1H-indole-2-yl)methanone,

1-(4-benzyloxypiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone,

1-(4-benzylpiperidine-1-yl)-1-(4-hydroxy-1H-indole-2-yl)methanone,

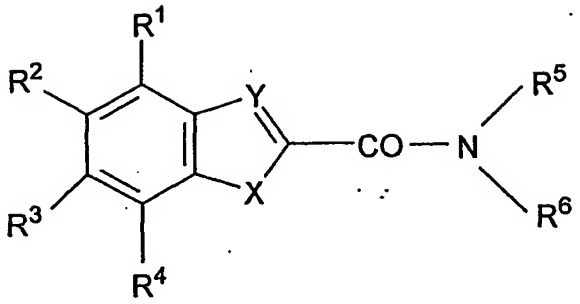
1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone,

1-(4-benzylpiperidine-1-yl)-1-(5-hydroxy-1H-indole-2-yl)methanone,

1-(6-hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyloxy)piperidine-1-yl)]methanone,
1-(4-benzylpiperidine-1-yl)-1-(5,7-dihydroxy-1H-indole-2-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-(4-phenoxymethylpiperidine-1-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-[4-(4-methylbenzyl)-4-hydroxypiperidine-1-yl)]methanone,
1-(4-benzylpiperidine-1-yl)-1-(6-hydroxy-7-methoxy-1H-indole-2-yl)methanone,
1-(6-acetoxy-1H-indole-2-yl)-1-(4-benzylpiperidine-1-yl)methanone,
1-[4-(4-fluorobenzylpiperidine-1-yl)]-1-(6-hydroxy-1H-indole-2-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-(4-phenoxypiperidine-1-yl)methanone,
1-[4-(4-fluorobenzylpiperidine-1-yl)]-1-(5-hydroxy-1H-indole-2-yl)methanone,
1-(4-hydroxy-1H-indole-2-yl)-1-(4-phenoxymethylpiperidine-1-yl)methanone,
1-(6-hydroxy-1H-indole-2-yl)-1-(4-phenoxy-3,6-dihydro-2H-piridine-1-yl)methanone,
1-(4-benzyloxypirrolidine-1-yl)-1-(6-hydroxy-1H-indole-2-yl)methanone,
1-[4-(4-chlorobenzyloxy)-piperidine-1-yl)]-1-(6-hydroxy-1H-indol-2-il)methanone,
6-hydroxy-1H-indole-2-carboxylic acid 4-phenylbuthylamide,
(4-benzylpiperidine-1-yl)-(6-hydroxy-1H-benzoimidazol-2-yl)-methanone and
(6-hydroxy-1H-benzoimidazol-2-yl)-[4-(4-methyl-benzyl)-piperidine-1-yl]-methanone

as well as the salts thereof formed with acids or bases.

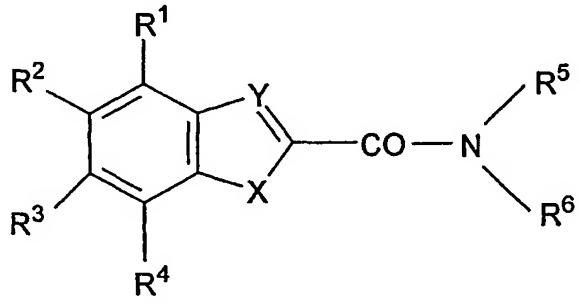
4. Pharmaceutical compositions having NR2B selective NMDA receptor antagonist effect, c h a r a c t e r i z e d b y comprising a biologically effective dose of a carboxylic acid amide derivative of formula (I) as active ingredient



(I)

– wherein the meaning of R^1, R^2, R^3, R^4, R^5, R^6, X and Y are as defined in claim 1 – and/or pharmaceutically acceptable salts thereof formed with acids or bases and carriers, filling materials and the like usually applied in pharmaceuticals.

5. Process for the synthesis of carboxylic acid amide derivatives of formula (I),

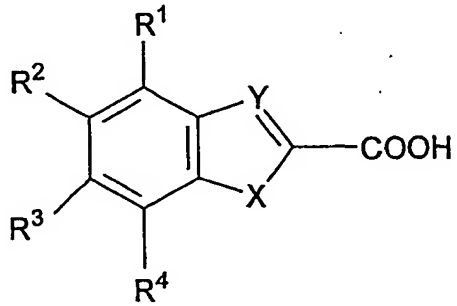


(I)

- wherein the meaning of R^1, R^2, R^3, R^4, R^5, R^6, X and Y are as defined in claim 1 -, as well as the racemates, optical antipodes and the salts thereof formed with acids and bases,

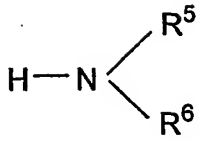
c h a r a c t e r i z e d b y

forming an amide bond between a carboxylic acid of formula (II)



(II)

- wherein the meaning of R^1, R^2, R^3, R^4, X and Y are as described in claim 1 – and an amine of formula (III)



(III)

wherein the meaning of R^5 and R^6 are as given in claim 1,

then the so obtained carboxylic acid amide derivative of formula (I) – wherein the meaning of R^1, R^2, R^3, R^4, R^5, R^6, X and Y is as defined in claim 1 – in given case is transformed into an other compound of formula (I) by introducing new substituents and/or modifying or removing the existing ones, and/or salt formation and/or liberating the compound from salts, and/or the obtained racemates are resolved using optical active acids or bases by known methods.

6. The process in claim 5, c h a r a c t e r i z e d b y reacting the acid of formula (II) - wherein the meaning of R^1, R^2, R^3, R^4, X and Y is as defined in claim 1 – as an active derivative in the amidation reaction.

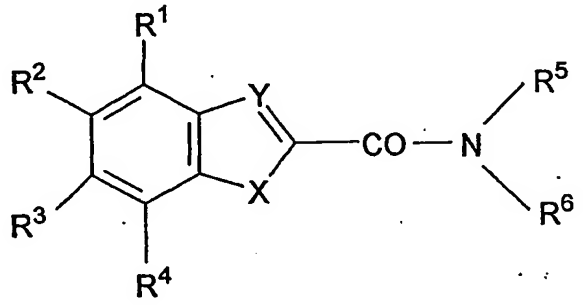
7. The process in claim 5, c h a r a c t e r i z e d b y reacting the acid of formula (II) - wherein the meaning of R^1, R^2, R^3, R^4, X and Y is as defined in claim 1 – as an active ester formed with O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate in the amidation reaction.

8. The process in claim 5, c h a r a c t e r i z e d b y reacting the acid of formula (II) - wherein the meaning of R^1, R^2, R^3, R^4, X and Y is as defined in claim 1 – as an acid halogenide in the amidation reaction.

9. The process in claim 8, c h a r a c t e r i z e d b y reacting the acid of formula (II) - wherein the meaning of R^1, R^2, R^3, R^4, X and Y is as defined in claim 1 – as acid chloride in the amidation reaction.

10. The process in claim 5, c h a r a c t e r i z e d b y reacting the acid of formula (II) - wherein the meaning of R^1, R^2, R^3, R^4, X and Y is as defined in claim 1 – as mixed anhydride formed with isobutyl chloroformate in the amidation reaction.

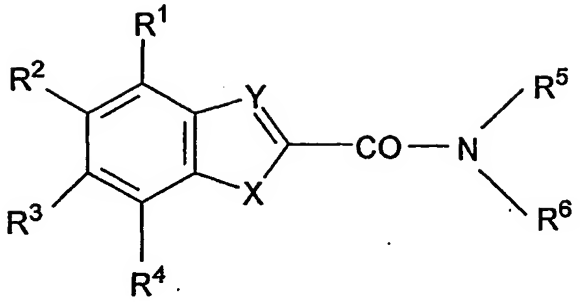
11. Process for manufacturing pharmaceutical compositions having NR2B selective NMDA receptor antagonist effect, c h a r a c t e r i z e d b y mixing a carboxylic acid amide derivative of formula (I),



(I)

– wherein the meaning of R^1, R^2, R^3, R^4, R^5, R^6, X and Y is as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or a pharmaceutically acceptable salts of it formed with acids or bases and carriers, filling materials and the like usually applied in pharmaceuticals.

12. Method of treatment and alleviation of symptoms of the following diseases of mammals – including human - chronic neurodegenerative disorders, such as stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, injury of spinal cord, epilepsy, anxiety, depression, cerebral ischemia of any origin, muscular spasm, multiinfarct dementia, injury of brain, pain (e.g. posttraumatic or postoperative) and chronic pain states, such as neuropathic pain or cancer related pain, migraine, human immunodeficiency virus (HIV) related neuronal injury, hypoglycemia, amyotrophic lateral sclerosis (ALS), bacterial sclerosis, maculadegeneration, degenerative disorders of the retina (e.g. CMV retinitis) asthma, tinnitus, aminoglycoside antibiotic-induced hearing loss, bacterial and viral infections, to decrease tolerance and/or dependence to drugs and alcohol, and for treatment of withdrawal syndrome of drugs and alcohol, psychosis, bladder incontinention, c h a r a c t e r i z e d b y administering effective amount/amounts of a carboxylic acid amide derivative of formula (I),



(I)

– wherein the meaning of R^1, R^2, R^3, R^4, R^5, R^6, X and Y is as defined in claim 1 – and/or the racemates, optical antipodes thereof and/or a pharmaceutically acceptable salts of it formed with acids or bases, to a mammal - including human – to be treated as such or suitably in the form of pharmaceutical composition manufactured with known auxiliaries usually applied in pharmaceuticals.

INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/HU 01/00099

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42 C07D235/24 C07D401/06 C07D405/06 C07D417/06
C07D498/04 C07D409/06 C07D211/16 A61K31/404 A61K31/4523
A61K31/445 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 42213 A (UNIV NEW YORK) 20 July 2000 (2000-07-20) claims 37,38,44,46,49,64,65; examples; tables 6,7	1,2,4
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; NANTKA-NAMIRSKI, PAWEL ET AL: "Derivatives of 2-carbethoxyindole. III. Products of amidation and alkylation of 5-benzyloxy- and 5-methoxy-2-carbethoxyindole" retrieved from STN Database accession no. 83:58582 XP002191278 compounds with RN=56242-58-1; 28837-72-1 & ACTA POL. PHARM. (1974), 31(5), 569-76 ,	1,2

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2002	11/03/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, B

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INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/HU 01/00099

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 105 763 A (KOWA CO) 18 April 1984 (1984-04-18) page 12, line 21 - line 22	1,2
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BETRABET, ASHOK M. ET AL: "Synthesis and pharmacology of 5-methoxyindole-2-carboxyamides and their 3-formyl derivatives" retrieved from STN Database accession no. 73:98724 XP002191279 compound with RN=28837-72-1 & INDIAN J. CHEM. (1970), 8(8), 704-6 ,	1,2
X	SCHEUERMAN R A ET AL: "The reduction of aromatic nitro groups on solid supports using sodium hydrosulfite (Na2S2O4)" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 41, no. 34, 19 August 2000 (2000-08-19), pages 6531-6535, XP004215808 ISSN: 0040-4039 7-amino-N-(phenylmethyl)-1H-Indole-2-carboxamide (implitly disclosed) page 6532; table 1	1,2
A	WO 98 14427 A (HOECHST MARION ROUSSEL INC) 9 April 1998 (1998-04-09) abstract	1,4,12
A	LUBISCH, W. ET AL: "Synthesis and biological evaluation of novel piperidine carboxamide derived calpain inhibitors" BIOORG. MED. CHEM. LETT. (2000), 10(19), 2187-2191 , XP004212000 page 2190, left-hand column; table 1	1,4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,4-12 (all in part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.
Furthermore it is not clear what the term "in given case substituted" (used several times in claim 1) means.

Consequently, the search was only complete for the examples mentioned in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ıal Application No
PCT/HU 01/00099

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		ZA 9708602 A	30-03-1998